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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03  JAPIO has been reloaded and enhanced

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'HOME' ENTERED AT 18:24:56 ON 11 SEP 2002

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=> FIL BIOSIS MEDLINE CAPLUS EMBASE SCISEARCH
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 7.14       7.14

FILE 'BIOSIS' ENTERED AT 18:45:26 ON 11 SEP 2002
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FILE 'SCISEARCH' ENTERED AT 18:45:26 ON 11 SEP 2002
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=> s (factor (W) VIIa)
L1         6206 (FACTOR (W) VIIA)

=> s l1 (W)(purity or purification or stable or stablize or purified storeage or store)
L2            8 L1 (W)(PURITY OR PURIFICATION OR STABLE OR STABLIZE OR PURIFIED
                STOREAGE OR STORE)

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=> d py so ti ab au 1-8 l2

L2   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2002 ACS
PY   2000
SO   Thrombosis and Haemostasis (2000), 83(1), 60-64
     CODEN: THHADQ; ISSN: 0340-6245
TI   Purification and characterization of factor VII inhibitor found in a
     patient with life threatening bleeding
AB   We recently obsd. a patient with acquired inhibitor-induced F.VII
     deficiency whose plasma level of F.VII was < 1.0%.  However, the biochem.
     nature of the inhibitor has not yet been clarified.  In the present study,
     we purified the F.VII inhibitor from the patient's plasma by using
     activated F.VII (F.VIIa)-conjugated gel and characterized the inhibitor.
     The results showed that the inhibitor comprised two kinds of antibodies:
     one was eluted with EDTA (antibody 1) and the other with glycine-HCl
     buffer (pH 2.3) (antibody 2) from the F.VIIa affinity gel.
     SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting anal.
     of these inhibitors demonstrated that both antibodies had features of IgG1
     (IgG1) with .kappa. and .lambda.-light chains.  Antibody 1 bound to the
     immobilized F.VIIa with a high affinity in the presence of calcium ion,
     while antibody 2 bound to the F.VIIa very weakly and the binding was
     independent of calcium ion.  Immunoblotting anal. demonstrated that
     antibody 1 bound to the light chain of F.VIIa after redn. with
     2-mercaptoethanol, while it did not react with either the
     .gamma.-carboxyglutamic acid (Gla)-domainless light chain of F.VIIa or the
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heavy chain with the protease domain. Antibody 1 markedly inhibited the activity of tissue factor-F.VIIa complex. Based on these observations, it is suggested that F.VIIa autoantibody (antibody 1) recognizes the calcium-dependent conformation within or near the Gla domain and inhibits F.VIIa activity by interacting with the light chain.
AU Kamikubo, Yuichi; Miyamoto, Seiji; Iwasa, Atsushi; Ishii, Masao; Okajima, Kenji

L2 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1997
1998
2002
1997
1997
1999
1997
1997
2001
SO Eur. Pat. Appl., 4 pp.
CODEN: EPXXDW
TI Purification of factor VII and activated factor VII using binding by immobilized soluble thromboplastin
AB This invention comprises a method for purifn. of blood-coagulation factor VII and/or factor VIIa using its binding by immobilized sol. thromboplastin. Ca2+ is present during factor VII binding by immobilized thromboplastin. Other potentially active factors are inactivated by antithrombin III and heparin and protamine sulfate may also be added if necessary. Bound factor VII or VIIa is eluted using a chelation agent such as citrate, oxalate, tartrate, NTA, EDTA, or EGTA.
IN Roemisch, Juergen; Stoehr, Hans-Arnold; Feussner, Annette

L2 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1995
1998
1995
1997
1995
1995
1995
2002
1995
2000
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
TI Stable preparation for the treatment of blood coagulation disorders comprising an activated coagulation factor and lipid vesicles
AB A stable prepn comprises a protein that is bound in and/or on lipid vesicles and that is treated for the inactivation of potentially present viruses. Further, the invention relates to methods for the prodn. of a stable prepn. for the treatment of blood coagulation disorder, wherein a protein is bound in and/or on lipid vesicles, and the method comprises a step in which the protein lipid complex is subjected to a treatment for the inactivation of potentially present viruses. A lyophilizate comprising factor Xa 1000 U, 1,2-dioleoyl-sn-glycero-3-phosphocholine 40.0, and 1,2-dioleoyl-sn-glycerophosphate 10.0 was taken up with water in the original vol. and extruded at 20.degree. through two-stacked 400 nm polycarbonate filters to obtain vesicles having av. diam. of .apprx.450nm. The efficacy of the vesicles in coagulation shortening of FVIII inhibitor plasma was shown.
IN Eibl, Johann; Schwartz, Hans-Peter; Siekmann, Juregen; Turecek, Peter

L2 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1995
1998
1995
1997
1995
1995
1995
2002
1996
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
TI Stable preparation for the treatment of blood coagulation disorders comprising an activated coagulation factor and lipid vesicles
AB A stable prepn. for the treatment of blood coagulation disorders comprises an active coagulation promoting substance, such as an activated coagulation factor, and optionally other proteins which are bound in or on lipid vesicles. The prepns. can be made available in a virus inactivated form. The invention also relates to the use of lipid vesicles which are bound with thrombocyte-like blood coagulation factors for the prodn. of a prepn. for the treatment of blood coagulation disorders which are connected with a lack of activated thrombocytes. A lyophilizate comprising factor Xa 1000 U, 1,2-dioleoyl-sn-glycero-3-phosphocholine 40.0, and 1,2-dioleoyl-sn-glycerophosphate 10.0 was taken up with water in the original vol. and extruded at 20.degree. through two-stacked 400 nm polycarbonate filters to obtain vesicles having av. diam. of .apprx.450nm. The efficacy of the vesicles in coagulation shortening of FVIII inhibitor plasma was shown.
IN Eibl, Johann; Schwartz, Hans Peter; Siekmann, Juergen; Turecek, Peter

L2 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1993
1996
1993
1995
1996
1997
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1996
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
TI Process for preparing an activated factor VII concentrate having a high purity from human plasma
AB Factor VIIa is prepd. from plasma, preferably human plasma, from which cryoppts. have been removed. The plasma is subjected to anion-exchange chromatog. and activation of factor VII is accomplished without addn. of exogenous protein. Factor VIIa essentially free of vitamin K-dependent factors, factor VIIIc, and factor VIIIcAg; in ratio of factor VIIa to factor VII of >5; and with a specific activity >200 IU/mg protein is produced by this process.
IN Dazey, Bernard; Hamsany, Mohamed; Enfedaque-Morer, Sylvia

L2 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1989
1995
1989
1992
1989
1990
1995

SO Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
TI Preparation of blood-coagulation factor VIIa using an adsorbent having affinity for calcium-binding proteins
AB A fraction rich in factor VIIa is prepd. for medicaments by adsorption on an adsorbent having an affinity for Ca-binding proteins (chosen from divalent metal salts that are insol. in H2O) and eluting with a buffer contg. sol. salts capable of displacing the adsorbed proteins. Factor VII is activated to factor VIIa with, e.g. celite and kaolin. The soln. may be incubated with a nonionic detergent and a solvent for virial membranes to inactivate any contaminating viruses. A nonutilized subfraction obtained in the prepn. of prothrombin complex and which was high in factors VII and VIIa was filter-sterilized, ultrafiltered in the presence of aprotinin (kallikrein inhibitor), adjusted to appropriate pH, and agitated with Ca3(PO4)2 for 40 min at ambient temp. The mixt. was centrifuged and the supernatant was removed. The ppt. was washed and factor VII was eluted with a pH 8 soln. contg. NaH2PO4 0.25, Na2HPO4 0.25, and NaCl 0.4 M. The eluate was concd., dialyzed, and treated with 1% Tween-0.3% n-tributyl phosphate for virus inactivation. The inactivating mixt. was sepd. from factor VII by adsorption of the factor on QAE-Sepharose.
IN Chabbat, Jacques; Pejaudier, Lucette; Steinbuch, Marion

L2 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1983
1983
1985
1983
1983
1992
1983
1987
1987
1983
1983
1983
1984
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
TI Treating a patient using hemostatic agent factor VIIa
AB Patients having blood clotting factor deficiency can be treated by the administration of compns. contg. hemostatic amts. of factor VIIa [65312-43-8]. The factor VIIa does not require the administration of any other activated or unactivated factors to be effective in achieving hemostasis. Thus, factor VIIa was prepd. from human plasma. The factor XIIa used in the activation was inhibited by the addn. of rabbit antiserum raised against human factor XII. The purified factor VII prior to activation contained 3250 units of factor VII/mg of protein. After purifn., the activity was increased 10-fold. The factor VIIa thus generated was used within 2 h but could be used successfully within 72 h if stored at 8.degree.. The effectiveness of factor VIIa in stopping bleeding was demonstrated in hemophilic dogs.
IN Thomas, William R.

L2 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS
PY 1981
SO Thromb. Res. (1981), 22(3), 375-80
CODEN: THBRAA; ISSN: 0049-3848
TI Isolation and characterization of human factor VIIa
AB Factor VIIa was purified from human plasma by Ba citrate adsorption and elution, (NH4)2SO4 fractionation, DEAE-Sephadex chromatog., Sephadex G-150

chromatog., and preparative polyacrylamide gel electrophoresis. Throughout the purifn. procedure, 10-20 mM benzamidine was used to minimize activation and degrdn. of factor VII. In spite of this, some prepns. yielded only factor VIIa, whereas others yielded single-chain factor VII with trace amts. of factor VIIa. The final prepn. of VIIa was homogeneous on SDS-gel electrophoresis, and the mol. wt. estd. for the unreduced protein was 50,000. After redn. with 2-mercaptoethanol, a heavy chain of 34,000 mol. wt. and a light chain of 24,000 mol. wt. were obsd. Expts. with di-isoPr fluorophosphate indicated that the binding site for the di-isoPr phosphoryl group in factor VIIa is present in the heavy chain. The partial N-terminal amino acid sequences of the heavy and light chains were also detd. The light chain of human factor VIIa apparently originates from the N-terminus of the precursor protein, and the heavy chain, from the C-terminal region of the precursor mol.

AU Kisiel, Walter; McMullen, Brad A.

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(FILE 'HOME' ENTERED AT 18:24:56 ON 11 SEP 2002)

FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE, SCISEARCH' ENTERED AT 18:45:26 ON 11 SEP 2002

L1 6206 S (FACTOR (W) VIIA)
L2 8 S L1 (W)(PURITY OR PURIFICATION OR STABLE OR STABLIZE OR PURIFI

=> s l1 (W)(specific (w) activity)
L3 0 L1 (W)(SPECIFIC (W) ACTIVITY)

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---Logging off of STN---

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	40.60	47.74
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.96	-4.96

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
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 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
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 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
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 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
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                  now available on STN
 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
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 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
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               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)
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=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

08/03/01

FILE 'REGISTRY' ENTERED AT 13:05:29 ON 12 SEP 2002

STRUCTURE FILE UPDATES: 11 SEP 2002 HIGHEST RN 449727-69-9
DICTIONARY FILE UPDATES: 11 SEP 2002 HIGHEST RN 449727-69-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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=> d l1 all

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 102786-61-8 REGISTRY
CN Blood-coagulation factor VIIa (human clone .lambda.HVII2463 protein moiety) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Eptacog alfa (activated)
CN **NovoSeven**
FS PROTEIN SEQUENCE
SQL 406,254,152
NTE multichain
modified (modifications unspecified)

type	------ location ------		description
bridge	Cys-7	- Cys-12	disulfide bridge
bridge	Cys-26	- Cys-42	disulfide bridge
bridge	Cys-110	- Cys-135'	disulfide bridge
bridge	Cys-158	- Cys-177	disulfide bridge
bridge	Cys-188	- Cys-216	disulfide bridge
bridge	Cys-17'	- Cys-22'	disulfide bridge
bridge	Cys-50'	- Cys-61'	disulfide bridge
bridge	Cys-55'	- Cys-70'	disulfide bridge
bridge	Cys-72'	- Cys-81'	disulfide bridge
bridge	Cys-91'	- Cys-102'	disulfide bridge
bridge	Cys-98'	- Cys-112'	disulfide bridge
bridge	Cys-114'	- Cys-127'	disulfide bridge
uncommon	Gla-6'	-	-
uncommon	Gla-7'	-	-
uncommon	Gla-14'	-	-
uncommon	Gla-16'	-	-
uncommon	Gla-19'	-	-
uncommon	Gla-20'	-	-
uncommon	Gla-25'	-	-
uncommon	Gla-26'	-	-
uncommon	Gla-29'	-	-

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uncommon Gla-35' - -

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SEQ      1 IVGGKVCPKG ECPWQVLLLV NGAQLCGGTL INTIWVVSAA HCFDKIKNWR
        51 NLIAVLGEHD LSEHDGDEQS RRVAQVIIPS TYVPGTTNHD IALLRLHQPV
       101 VLTDHVVPLC LPERTFSERT LAFVRFSLVS GWGQLLDRGA TALELMVLNV
       151 PRLMTQDCLQ QSRKVGDSPN ITEYMFCAGY SDGSKDSCKG DSGGPHATHY
       201 RGTWYLTGIV SWGQGCATVG HFGVYTRVSQ YIEWLQKLMR SEPRPGVLLR
       251 APFP

SEQ      1 ANAFLXXLRP GSLXRXCKXX QCSFXXARXI FKDAXRTKLF WISYSDGDQC
        51 ASSPCQNGGS CKDQLQSYIC FCLPAFEGRN CETHKDDQLI CVNENGGCEQ
       101 YCSDHTGTKR SCRCHEGYSL LADGVSCTPT VEYPCGKIPI LEKRNASKPQ
       151 GR

SEQ3     1 Ile-Val-Gly-Gly-Lys-Val-Cys-Pro-Lys-Gly-
        11 Glu-Cys-Pro-Trp-Gln-Val-Leu-Leu-Leu-Val-
        21 Asn-Gly-Ala-Gln-Leu-Cys-Gly-Gly-Thr-Leu-
        31 Ile-Asn-Thr-Ile-Trp-Val-Val-Ser-Ala-Ala-
        41 His-Cys-Phe-Asp-Lys-Ile-Lys-Asn-Trp-Arg-
        51 Asn-Leu-Ile-Ala-Val-Leu-Gly-Glu-His-Asp-
        61 Leu-Ser-Glu-His-Asp-Gly-Asp-Glu-Gln-Ser-
        71 Arg-Arg-Val-Ala-Gln-Val-Ile-Ile-Pro-Ser-
        81 Thr-Tyr-Val-Pro-Gly-Thr-Thr-Asn-His-Asp-
        91 Ile-Ala-Leu-Leu-Arg-Leu-His-Gln-Pro-Val-
       101 Val-Leu-Thr-Asp-His-Val-Val-Pro-Leu-Cys-
       111 Leu-Pro-Glu-Arg-Thr-Phe-Ser-Glu-Arg-Thr-
       121 Leu-Ala-Phe-Val-Arg-Phe-Ser-Leu-Val-Ser-
       131 Gly-Trp-Gly-Gln-Leu-Leu-Asp-Arg-Gly-Ala-
       141 Thr-Ala-Leu-Glu-Leu-Met-Val-Leu-Asn-Val-
       151 Pro-Arg-Leu-Met-Thr-Gln-Asp-Cys-Leu-Gln-
       161 Gln-Ser-Arg-Lys-Val-Gly-Asp-Ser-Pro-Asn-
       171 Ile-Thr-Glu-Tyr-Met-Phe-Cys-Ala-Gly-Tyr-
       181 Ser-Asp-Gly-Ser-Lys-Asp-Ser-Cys-Lys-Gly-
       191 Asp-Ser-Gly-Gly-Pro-His-Ala-Thr-His-Tyr-
       201 Arg-Gly-Thr-Trp-Tyr-Leu-Thr-Gly-Ile-Val-
       211 Ser-Trp-Gly-Gln-Gly-Cys-Ala-Thr-Val-Gly-
       221 His-Phe-Gly-Val-Tyr-Thr-Arg-Val-Ser-Gln-
       231 Tyr-Ile-Glu-Trp-Leu-Gln-Lys-Leu-Met-Arg-
       241 Ser-Glu-Pro-Arg-Pro-Gly-Val-Leu-Leu-Arg-
       251 Ala-Pro-Phe-Pro

SEQ3     1 Ala-Asn-Ala-Phe-Leu-Gla-Gla-Leu-Arg-Pro-
        11 Gly-Ser-Leu-Gla-Arg-Gla-Cys-Lys-Gla-Gla-
        21 Gln-Cys-Ser-Phe-Gla-Gla-Ala-Arg-Gla-Ile-
        31 Phe-Lys-Asp-Ala-Gla-Arg-Thr-Lys-Leu-Phe-
        41 Trp-Ile-Ser-Tyr-Ser-Asp-Gly-Asp-Gln-Cys-
        51 Ala-Ser-Ser-Pro-Cys-Gln-Asn-Gly-Gly-Ser-
        61 Cys-Lys-Asp-Gln-Leu-Gln-Ser-Tyr-Ile-Cys-
        71 Phe-Cys-Leu-Pro-Ala-Phe-Glu-Gly-Arg-Asn-
        81 Cys-Glu-Thr-His-Lys-Asp-Asp-Gln-Leu-Ile-
        91 Cys-Val-Asn-Glu-Asn-Gly-Gly-Cys-Glu-Gln-
       101 Tyr-Cys-Ser-Asp-His-Thr-Gly-Thr-Lys-Arg-
       111 Ser-Cys-Arg-Cys-His-Glu-Gly-Tyr-Ser-Leu-
       121 Leu-Ala-Asp-Gly-Val-Ser-Cys-Thr-Pro-Thr-
       131 Val-Glu-Tyr-Pro-Cys-Gly-Lys-Ile-Pro-Ile-
       141 Leu-Glu-Lys-Arg-Asn-Ala-Ser-Lys-Pro-Gln-
       151 Gly-Arg
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DR 151821-07-7
MF Unspecified

08/03/01

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CI MAN
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CIN, DIOGENES, PHAR, PROMT, TOXCENTER, USAN, USPAT2, USPATFULL
39 REFERENCES IN FILE CA (1967 TO DATE)
39 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1

AN 137:149992 CA
TI Possible synergy between recombinant factor VIIa and prothrombin complex concentrate in hemophilia therapy
AU Key, Nigel S.; Christie, Beverly; Henderson, Nicole; Nelsestuen, Gary L.
CS Department of Medicine, University of Minnesota, Minneapolis, MN, USA
SO Thrombosis and Haemostasis (2002), 88(1), 60-65
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer GmbH
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Recombinant factor VIIa (rFVIIa; Novoseven) is used for treatment of hemophilia patients with inhibitors. There are poorly defined differences in clin. responsiveness between individuals. Prior to licensure in the United States, rFVIIa was available through the compassionate use program, during which two patients described in this study demonstrated an excellent response. More recently, one of these individuals showed a sub-optimal response to rFVIIa. One possible explanation for different treatment outcomes was sequential therapy with prothrombin complex concs. (PCC) followed by rFVIIa in the compassionate use program. In support of this, an in vitro test showed that this patient had an exceptionally strong response to rFVIIa when it was added to whole blood after the patient received PCC therapy. Results with other patients supported this hypothesis. With further evaluation, a therapeutic approach combining sequential PCC and rFVIIa may prove useful for treatment of bleeding refractory to either agent used alone.
ST factor VIIa prothrombin hemostatic hemophilia
IT Blood coagulation
(disseminated intravascular; possible synergy between recombinant factor VIIa and prothrombin complex conc. in hemophilia therapy)
IT Hemophilia
Hemorrhage
Hemostatics
Human
Thrombus
(possible synergy between recombinant factor VIIa and prothrombin complex conc. in hemophilia therapy)
IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(possible synergy between recombinant factor VIIa and prothrombin complex conc. in hemophilia therapy)
IT Drug interactions
(synergistic; possible synergy between recombinant factor VIIa and prothrombin complex conc. in hemophilia therapy)
IT 9001-26-7, Prothrombin complex 65312-43-8, Factor VIIa 102786-61-8, Novoseven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(possible synergy between recombinant factor VIIa and prothrombin complex conc. in hemophilia therapy)
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
(1) Aledort, L; Thromb Haemost 2000, V83, P637 CAPLUS

(2) Clauss, A; Acta Haematol 1957, V17, P237 CAPLUS
(3) Hedner, U; Blood Coagul Fibrinolysis 2000, V11(suppl 1), PS107
(4) Henderson, N; Thromb Haemost 2002, V88, P98 CAPLUS
(5) Key, N; Thromb Haemost 1998, V80, P912 CAPLUS
(6) Lindley, C; Clin Pharmacol Therapeut 1994, V55, P638 CAPLUS
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REFERENCE 2

AN 137:41499 CA
TI Prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa
AU Young, Guy; Nugent, Diane J.
CS Division of Hematology, Children's Hospital of Orange County, Orange, CA, USA
SO Hematology (Reading, United Kingdom) (2001), 6(5), 341-346
CODEN: HMATFL; ISSN: 1024-5332
PB Taylor & Francis Ltd.
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Recombinant factor VIIa [rFVIIa (Novoseven, Novo Nordisk, Bagsvaerd, Denmark)] is a novel therapy used to treat hemophiliacs with inhibitors and bleeding. Coagulopathy with severe factor VII deficiency is common in liver failure, and liver biopsies are often required in these patients; however, there is a high risk of bleeding complications. In one report, 12.5% of children with coagulopathy and 0.8% of children without coagulopathy had bleeding complications after liver biopsy. Other reports have demonstrated increased bleeding after liver biopsy in patients with bleeding disorders. Std. treatment for such patients includes fresh frozen plasma (FFP) and prothrombin complex concs. (PCC), both of which have significant limitations. In order to achieve hemostatic factor levels, large vols. of FFP are required which may not be tolerated, esp. in young children and patients with liver failure. PCC can cause DIC, esp. in liver failure and carry a risk of viral transmission. We have performed liver biopsies and central venous catheter (CVC) placement in three neonates with liver failure utilizing rFVIIa to prevent bleeding complications. All three patients had mild gastrointestinal (GI) bleeding prior to surgery which did not respond to FFP and cryoppt. (cryo). None of the patients had bleeding complications. These cases demonstrate the utility of using rFVIIa in neonates with liver failure undergoing liver biopsy and CVC placement. Our choice of rFVIIa rather than PCC was based on selecting an agent that targets the deficiency of factor VII, concerns for disseminated intravascular coagulation, and the risk of transmitting infectious agents from plasma products. In conclusion, we recommend the use of rFVIIa for prevention of bleeding complications prior to surgery in patients with liver failure.
ST Novoseven factor VIIa hemostatic bleeding neonate liver failure biopsy
IT Liver
(biopsy; prevention of bleeding complications in neonates with liver

failure undergoing surgery using recombinant factor VIIa)
IT Medical goods
(catheters, venous; prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa)
IT Blood coagulation
(disorder; prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa)
IT Liver, disease
(failure; prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa)
IT Coagulation
Hemorrhage
Hemostatics
Human
Newborn
(prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa)
IT 65312-43-8, Factor VIIa 102786-61-8, Novoseven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa)
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
(1) Bernstein, D; Gastroenterology 1997, V113, P1930 MEDLINE
(2) Erhardtsen, E; Blood Coag Fibrin 1998, V9, P741 CAPLUS
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REFERENCE 3

AN 137:463 CA
TI Use of recombinant factor VIIa to treat persistent bleeding following dental extractions in two cirrhotic patients
AU Berthier, A.-M.; Guillygomarc'h, A.; Messner, M.; Pommereuil, M.; Bader, G.; De Mello, G.
CS Department of Haematology, University Hospital, Rennes, F-35033, Fr.
SO Vox Sanguinis (2002), 82(3), 119-121
CODEN: VOSAAD; ISSN: 0042-9007
PB Blackwell Publishing Ltd.
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Background and Objectives: A single dose of recombinant factor VIIa (rFVIIa) has been shown to be effective and safe in correcting the prothrombin time (PT) in cirrhotic patients, but no clin. data exists demonstrating its efficacy in arresting active bleeding. Materials and Methods: rFVIIa was used in two cirrhotic patients for persistent bleeding following dental extns. despite repeated treatment at the wound site and, in one case, repeated administrations of fresh-frozen plasma (FFP). Results: Bleeding stopped promptly in both patients after administration of rFVIIa. However, bleeding recurred in the patient who had not received concomitant treatment at the extn. sites. No recurrence of bleeding was

obsd. in the second patient, who underwent local treatment 15 min after rFVIIa. Conclusions: Recombinant factor VIIa arrested bleeding after dental extns. in two cirrhotic patients who had been unsuccessfully treated with FFP. However, addnl. local treatment is needed to limit the risk of recurrence as a result of the short half-life of rFVIIa.

ST factor VIIa hemostatic dental extn cirrhosis

IT Surgery
(dental extn.; use of recombinant factor VIIa to treat persistent bleeding following dental extns. in two humans with cirrhosis)

IT Cirrhosis
Hemostatics
Human
(use of recombinant factor VIIa to treat persistent bleeding following dental extns. in two humans with cirrhosis)

IT 102786-61-8, NovoSeven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of recombinant factor VIIa to treat persistent bleeding following dental extns. in two humans with cirrhosis)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

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REFERENCE 4

AN 136:379313 CA

TI Recombinant activated factor VII (rFVIIa): characterization, manufacturing, and clinical development

AU Jurlander, Birgit; Thim, Lars; Klausen, Niels K.; Persson, Egon; Kjalke, Marianne; Rexen, Per; Jorgensen, Tom B.; Ostergaard, Per B.; Erhardtsen, Elisabeth; Bjorn, Soren E.

CS IO Biopharm, Novo Nordisk A/S, Lyngby, Den.

SO Seminars in Thrombosis and Hemostasis (2001), 27(4), 373-383
CODEN: STHMBV; ISSN: 0094-6176

PB Thieme Medical Publishers, Inc.

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review. Recombinant activated coagulation factor VII (rFVIIa) (NovoSeven) was developed for treatment of bleeding in hemophilia patients with inhibitors (antibodies) against factors VIII or IX. RFVIIa initiates the coagulation cascade by binding to tissue factor at the site of injury and causes the formation of sufficient amts. of thrombin to trigger coagulation. Patients with a variety of other coagulation deficiencies than hemophilia characterized by an impaired thrombin generation and life-threatening bleeding have been reported as successfully treated with rFVIIa. Data are now entered into clin. registries established to further monitor this exptl. treatment with NovoSeven. RFVIIa is produced free of any added human protein. The amino acid sequence of rFVIIa is identical to plasma-derived FVIIa (pdFVIIa). Posttranslational modifications (i.e., .gamma.-carboxylations, N- and O-glycosylations) are qual. identical in pdFVIIa and rFVIIa although some quant. differences exist. The activities of rFVIIa and pdFVIIa are indistinguishable. Manufg. of rFVIIa involves expression in baby hamster kidney (BHK) cells followed by purifn., including three ion-exchange and one immunoaffinity chromatog. steps. The last anion-exchange chromatog. step ensures completion of the autoactivation of recombinant factor VII (rFVII) to rFVIIa. This review

describes the mechanism of action, characterization, manufg., and preclin. and current clin. evidence for the efficacy and safety of rFVIIa.
ST review coagulation factor VII hemophilia
IT Databases
(clin. registries; recombinant activated factor VII (rFVIIa): characterization, manufg., and clin. development)
IT Hemophilia
Human
(recombinant activated factor VII (rFVIIa): characterization, manufg., and clin. development)
IT 9001-25-6P, Blood-coagulation factor VII 102786-61-8P, NovoSeven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(recombinant activated factor VII (rFVIIa): characterization, manufg., and clin. development)
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REFERENCE 5

AN 136:252567 CA
TI Methods for drug administration and distribution based on monitoring blood viscosity and other parameters for diagnostics and treatment
IN Kensey, Kenneth
PA USA
SO U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 819,924.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-00
ICS A61B005-00
NCL 514001000
CC 63-8 (Pharmaceuticals)
Section cross-reference(s): 1, 14
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002032149	A1	20020314	US 2001-841389	20010424
	CA 2301161	AA	19990304	CA 1998-2301161	19980826
	JP 2001514384	T2	20010911	JP 2000-507994	19980826
	NO 2000000944	A	20000225	NO 2000-944	20000225
	US 2001039828	A1	20011115	US 2001-789350	20010221
	US 2002007664	A1	20020124	US 2001-897164	20010702
	US 2002088953	A1	20020711	US 2001-33841	20011227
PRAI	US 1997-919906	19970828			
	US 1999-439795	19991112			
	US 2000-501856	20000210			
	US 2000-628401	20000801			

US 2000-727950 20001201
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WO 1998-US17657 19980826
KR 2000-16044 20000329
US 2000-615340 20000712
US 2000-228612P 20000828
US 2001-789350 20010221

AB Various methods are provided for detg. and utilizing the viscosity of the circulating blood of a living being, i.e., a human, over a range of shear rates for diagnostics and treatment, such as detecting/reducing blood viscosity, work of the heart, contractility of the heart, for detecting/reducing the surface tension of the blood, for detecting plasma viscosity, for explaining/countering endothelial cell dysfunction, for providing high and low blood vessel wall shear stress data, red blood cell deformability data, lubricity of blood, and for treating different ailments such as peripheral arterial disease in combination with administering to a living being at least one pharmaceutically acceptable agent. Agents pharmaceutically effective to regulate at least one of the afore mentioned blood parameters are used to adjust distribution of a substance through the bloodstream. For example, when blood viscosity is a blood flow parameter monitored, an agent is selected from i.v. diluents, red blood cell deformability agents, antiurea agents, oral contraceptives, antidiabetic agents, antiarrhythmics, antihypertensives, antihyperlipidemics, antiplatelet agents, appetite suppressants, antiobesity agents, blood modifiers, smoking deterrent agents, and nutritional supplements.

ST blood viscosity drug delivery diagnostic therapy

IT Saponification
(agents for; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Platelet (blood)
(aggregation; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Adrenoceptor antagonists
Agglutination
Antiarrhythmics
Anticholesteremic agents
Anticoagulants
Antidiabetic agents
Antihypertensives
Antiobesity agents
Appetite depressants
Blood analysis
Blood coagulation
Cardiac contraction
Circulation
Diagnosis
Drug delivery systems
Drug dependence
Drug targeting
Electrolytes, biological
Human
Hypolipemic agents
Platelet aggregation inhibitors
Sedimentation (separation)
Surfactants
Therapy
Thixotropy
Tobacco products
Vasodilators

(app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Amino acids, biological studies
Estrogens
Gelatins, biological studies
Hemoglobins
Immunoglobulins
Mineral elements, biological studies
Polyoxyalkylenes, biological studies
Progestogens
Thrombomodulin
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Glycerides, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood, lowering agents; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Viscosity
(blood; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Ion channel blockers
(calcium; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Shear stress
(circulating blood; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Clays, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(colloidal; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Erythrocyte
(deformability; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Tobacco smoke
(deterrent agents; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Blood vessel, disease
(endothelium, injury, shear; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Drug delivery systems
(enteric; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Thrombus
(formation and lysis time; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Biopolymers
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gels; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Drug delivery systems
(inhalants; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT Cell adhesion
(inhibitors; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Drug delivery systems
(injections, i.m.; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Drug delivery systems
(injections, i.v.; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Drug delivery systems
(injections, s.c.; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Contraceptives
(oral; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Drug delivery systems
(parenterals; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Cell aggregation
(platelet; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Bentonite, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodian, magma; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Magma
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodium bentonite; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Diet
(supplements; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Blood
(viscosity; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Heart
(work; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT Adrenoceptor antagonists
(.beta.-; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT 187741-48-6, CHF 1521
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CHF 1521; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT 57-13-6, Urea, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antiurea agents; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)
IT 50-28-2, Estradiol, biological studies 50-78-2, Aspirin 52-01-7, Spironolactone 52-53-9, Verapamil 54-11-5, Nicotine 54-31-9, Furosemide 55-63-0, Nitroglycerin 57-63-6, Ethinyl estradiol 58-32-2, Dipyridamole 58-54-8, Ethacrynic acid 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-66-5, Acetazolamide 68-22-4, Norethindrone 69-65-8, Mannitol 70-51-9 72-33-3, Mestranol 81-81-2, Warfarin 86-54-4, Hydralazine 87-33-2, Isosorbide dinitrate 94-20-2, Chlorpropamide 122-09-8, Phentermine 396-01-0, Triamterene 520-85-4,

Medroxyprogesterone 525-66-6, Propranolol 634-03-7, Phendimetrazine 637-07-0, Clofibrate 657-24-9, Metformin 797-63-7, Levonorgestrel 1156-19-0, Tolazamide 1231-93-2, Ethynodiol 2098-66-0, Cyproterone 3056-17-5, Stavudine 3930-20-9, Sotalol 4291-63-8, Cladribine 6533-00-2, Norgestrel 8001-27-2, Hirudin 9000-69-5, Pectin 9000-94-6, Antithrombin III 9002-01-1, Streptokinase 9002-18-0, Agar 9002-72-6, Somatotropin 9004-10-8, Insulin, biological studies 9004-54-0, Dextran, biological studies 9004-67-5, Methyl cellulose 9005-27-0, Hetastarch 9005-49-6, Enoxaparin, biological studies 9007-12-9, Calcitonin 9039-53-6, Urokinase 9041-08-1, OP 2000 10238-21-8, Glyburide 11041-12-6, Cholestyramine 12650-69-0, Mupirocin 13523-86-9, Pindolol 15291-77-7, Ginkgolide B 15307-86-5, Diclofenac 16051-77-7, Isosorbide mononitrate 17560-51-9, Metolazone 18559-94-9, Salbutamol 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 24967-94-0, Dermatan sulfate 25322-68-3, Polyethylene glycol 25614-03-3, Bromocriptine 25812-30-0, Gemfibrozil 26807-65-8, Indapamide 26839-75-8, Timolol 28395-03-1, Bumetanide 28523-86-6, Sevoflurane 28721-07-5, Oxcarbazepine 29094-61-9, Glipizide 29122-68-7, Atenolol 29457-07-6, Ticarcillin disodium 30516-87-1, Zidovudine 32222-06-3, Calcitriol 34391-04-3, Levosalbutamol 34580-13-7, Ketotifen 34911-55-2, Bupropion 35189-28-7, Norgestimate 38304-91-5, Minoxidil 39562-70-4, Nitrendipine 42200-33-9, Nadolol 42399-41-7, Diltiazem 42924-53-8, Nabumetone 47141-42-4, Levobunolol 49562-28-9, Fenofibrate 50925-79-6, Colestipol 51333-22-3, Budesonide 51384-51-1, Metoprolol 54024-22-5, Desogestrel 55142-85-3, Ticlopidine 55985-32-5, Nicardipine 56180-94-0, Acarbose 56211-40-6, Torsemide 56420-45-2, Epirubicin 59122-46-2, Misoprostol 60202-16-6, Blood-coagulation factor XIV 60282-87-3, Gestodene 62571-86-2, Captopril 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 64221-86-9, Imipenem 64544-07-6, Cefuroxime axetil 64706-54-3, Bepridil 66085-59-4, Nimodipine 66722-44-9, Bisoprolol 67227-56-9, Fenoldopam 68252-19-7, Pirmenol 68291-97-4, Zonisamide 69655-05-6, Didanosine 71119-11-4, Bucindolol 71486-22-1, Vinorelbine 72509-76-3, Felodipine 72956-09-3, Carvedilol 73573-87-2, Formoterol 73963-72-1, Cilostazol 74191-85-8, Doxazosin 74863-84-6, Argatroban 75330-75-5, Lovastatin 75695-93-1, Isradipine 75847-73-3, Enalapril 76547-98-3, Lisinopril 77191-36-7, Nefiracetam 78415-72-2, Milrinone 79350-37-1, Cefixime 79902-63-9, Simvastatin 80474-14-2, Fluticasone propionate 81732-65-2, Bambuterol 82410-32-0, Ganciclovir 82834-16-0, Perindopril 83869-56-1, Granulocyte-macrophage colony-stimulating factor 84057-84-1, Lamotrigine 84057-95-4, Ropivacaine 84449-90-1, Raloxifene 84625-59-2, Dotarizine 85441-61-8, Quinapril 86541-75-5, Benazepril 86780-90-7, Aranidipine 87239-81-4, Cefpodoxime proxetil 87333-19-5, Ramipril 87679-37-6, Trandolapril 88150-42-9, Amlodipine 89565-68-4, Tropisetron 90729-41-2, Oxodipine 91161-71-6, Terbinafine 92665-29-7, Cefprozil 93221-48-8, Levobetaxolol 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 94535-50-9, Lemakalim 94739-29-4, Lemildipine 95058-81-4, Gemcitabine 96036-03-2, Meropenem 96125-53-0, Clentiazem 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan 98048-97-6, Fosinopril 99522-79-9, Pranidipine 100427-26-7, Lercanidipine 100986-85-4, Levofloxacin 101526-83-4, Sematilide 102786-61-8, Blood-coagulation factor VIIa (human clone .lambda.HVII2463 protein moiety) 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 103745-39-7, Fasudil 103890-78-4, Lacidipine 104713-75-9, Barnidipine 105816-04-4, Nateglinide 105857-23-6, Alteplase 105979-17-7, Benidipine 106650-56-0, Sibutramine 107452-89-1, Ziconotide 109889-09-0, Granisetron 111025-46-8, Pioglitazone 112809-51-5, Letrozole 113665-84-2, Clopidogrel 113806-05-6, Olopatadine 114432-13-2, Fantofarone 114798-26-4, Losartan 114870-03-0, Fondaparinux sodium 115103-54-3, Tiagabine 115256-11-6, Dofetilide 116308-55-5, Watanidipine 117279-73-9, Israpafant 118457-14-0, Nebivolol 119684-0

5-8, Mesoglycan 120511-73-1, Anastrozole 120993-53-5, Desirudin 121181-53-1, Filgrastim 121679-13-8, Naratriptan 122647-31-8, Ibutilide 123524-52-7, Azelnidipine 123774-72-1, Sargramostim 123948-87-8, Topotecan 124750-99-8, Losartan potassium 124832-26-4, Valacyclovir 124937-51-5, Tolterodine 128270-60-0, Bivalirudin 128470-16-6, Arbutamine 129618-40-2, Nevirapine 130209-82-4, Latanoprost 130636-43-0, Nifekalant 131179-95-8, RSR 13 132579-32-9, Rocepafant 132875-61-7, Remifentanil 133040-01-4, Eprosartan 133242-30-5, Landiolol 133652-38-7, Reteplase 134308-13-7, Tolcapone 134523-00-5, Atorvastatin 134678-17-4, Lamivudine 134865-37-5, Meluadrine tartrate 135062-02-1, Repaglinide 136468-36-5, Foropafant 137862-53-4, Valsartan 138068-37-8, Lepirudin 138402-11-6, Irbesartan 138661-03-7, Furnidipine 143653-53-6, Abciximab 144494-65-5, Tirofiban 144689-63-4, Olmesartan medoxomil 144701-48-4, Telmisartan 145040-37-5, Candesartan cilexetil 145375-43-5, Mitiglinide 145599-86-6, Cerivastatin 147059-72-1, Trovafloxacin 147511-69-1, Pitavastatin 148883-56-1, Tifacogin 149908-53-2, Azimilide 150332-35-7, Pamaqueside 154189-24-9, ARC68397AA 158876-82-5, Rupatadine 159776-70-2, Melagatran 170902-47-3, Roxifiban 173324-94-2, Temiverine 187523-35-9, BMS204352
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT 188627-80-7, Eptifibatide 210101-16-9, Conivaptan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT 7631-86-9, Colloidal silica, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(colloidal; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT 9015-82-1, Angiotensin-converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microcryst.; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT 9001-26-7, Prothrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(rate; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

IT 6027-13-0, Homocysteine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reducing agents; app. and methods for monitoring blood viscosity and other parameters in drug delivery for diagnostics and treatment)

REFERENCE 6

AN 136:144439 CA
TI Continuous infusion of recombinant factor VIIa: continue or not?
AU Ewenstein, Bruce M.
CS Hematology Division, Brigham and Women's Hospital, Boston, MA, 02115, USA
SO Thrombosis and Haemostasis (2001), 86(4), 942-944
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer GmbH
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review presents various clin. studies on the effect of continuous

infusion (CI) of recombinant activated factor VIIa on patients with hemophilia. Clin. studies support the use of rFVIIa administration by CI so long as the substantial individual variations in clearance and hemostatic response are taken into consideration. Targeting rFVIIa:C levels to 30-40 IU/mL in the immediate post-operative period provide a margin of safety sufficient for most patients and in most clin. situations, while steady-state levels of less than 10 IU/mL are inadequate. The standardized factor VII:C one-stage clotting assay is used to monitor the FVII:C levels.

ST review factor VIIa Novoseven hemostatic hemophilia

IT Hemophilia
Hemostatics
Human
(continuous infusion of recombinant factor VIIa)

IT 102786-61-8, Novoseven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(continuous infusion of recombinant factor VIIa)

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REFERENCE 7

AN 136:95818 CA

TI Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with

09921880

factor VIII inhibitors

AU Santagostino, E.; Morfini, M.; Rocino, A.; Baudo, F.; Scaraggi, F. A.; Gringeri, A.

CS Angelo Bianchi Bonoml Hemophilia and Thrombosis Center, Department of Internal Medicine, IRCCS Maggiore Hospital and University of Milan, Naples, Italy

SO Thrombosis and Haemostasis (2001), 86(4), 954-958
CODEN: THHADQ; ISSN: 0340-6245

PB Schattauer GmbH

DT Journal

LA English

CC 1-8 (Pharmacology)

AB A multicenter prospective study of recombinant activated factor VII (rFVIIa) given by continuous infusion (CI) to treat severe hemorrhages and to handle surgical procedures was carried out. Relations between clin. efficacy, dosages used and levels of FVII coagulant activity (FVII:C) achieved in plasma were also evaluated. Case material included 25 patients with hemophilia (9 children and 16 adults) with high-responding inhibitors and 3 patients with acquired factor VIII inhibitors. Overall, 35 CI courses were given for 10 spontaneous bleeding episodes, 11 major surgical procedures and 14 minor surgical procedures. Bolus doses of 90 to 150 .mu.g/kg (median: 100) were followed by CI given at median rates of 20 .mu.g/kg/h for major surgery and of 17 and 16 .mu.g/kg/h for minor surgery and spontaneous hemorrhages. Satisfactory hemostasis was obtained in 30 of 35 courses (88%). RFVIIa CI was ineffective in 2 hemophiliacs undergoing surgical operations and in another hemophiliac with hemoperitoneum who had to be switched to other treatments (high doses of porcine or human factor VIII concs.). RFVIIa CI was partially effective in 2 hemophiliacs who had mild local bleeding after minor surgery. The CI rates and the corresponding FVII:C levels in plasma were similar in effective, partially effective and ineffective courses (median rate: 17, 20 and 20 .mu.g/kg/h, resp.; median FVII:C: 14, 18 and 18 IU/mL, resp.). A single adverse event was obsd., superficial thrombophlebitis. This study confirms that rFVIIa given by CI is effective in a high proportion of patients with factor VIII inhibitors. It also demonstrates that FVII:C levels attained in plasma do not always predict efficacy because similarly high levels were attained during successful treatments and in those that failed.

ST factor VIIa hemostatic hemophilia surgery

IT Hemophilia
Hemostatics
Human
Surgery
(relationship between factor VII activity and clin. efficacy of recombinant factor VIIa given by continuous infusion to humans with factor VIII inhibitors)

IT Hemorrhage
(spontaneous; relationship between factor VII activity and clin. efficacy of recombinant factor VIIa given by continuous infusion to humans with factor VIII inhibitors)

IT 9001-27-8, Blood coagulation factor VIII
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; relationship between factor VII activity and clin. efficacy of recombinant factor VIIa given by continuous infusion to humans with factor VIII inhibitors)

IT 102786-61-8, NovoSeven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(relationship between factor VII activity and clin. efficacy of recombinant factor VIIa given by continuous infusion to humans with factor VIII inhibitors)

IT 9001-25-6, Blood-coagulation factor VII
RL: BSU (Biological study, unclassified); BIOL (Biological study) (relationship between factor VII activity and clin. efficacy of recombinant factor VIIa given by continuous infusion to humans with factor VIII inhibitors)

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REFERENCE 8

AN 136:95817 CA
TI Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU/ml is associated with an increased incidence of bleeding
AU Smith, Mark P.; Ludlam, Christopher A.; Collins, Peter W.; Hay, Charles R. M.; Wilde, Jonathan T.; Grigeri, Alessandro; Melsen, Tina; Savidge, Geoffrey F.
CS Haemophilia Centre, Reference Centre for Haemostatic and Thrombotic Disorders, St Thomas' Hospital, London, SE1 7EH, UK
SO Thrombosis and Haemostasis (2001), 86(4), 949-953
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer GmbH
DT Journal
LA English
CC 1-8 (Pharmacology)
AB The authors examd. recombinant activated factor VII (rVIIa) administered by continuous infusion to eight patients with inhibitors to factor VIII, undergoing elective surgery. RVIIa was infused at a fixed rate of 16.5 .mu.g/kg/h for a median of 13.5 days (range 1-26). There was effective hemostasis at this infusion rate in only one of two minor procedures and two of six major operations. Three patients experienced excessive bleeding despite plasma factor VII activity around 10 IU/mL. Serious bleeding occurred in two other patients caused by procedural errors unrelated to rVIIa and required re-operation. The median rVIIa clearance on day 1 was 57 mL/h/kg (range 18-100) and on day 3 was 100 mL/h/kg (range 61-200). Clearance on the final infusion day was not significantly different from day 3. The infusion did not induce pathol. activation of the coagulation mechanism. The only thrombotic adverse events were two episodes of superficial thrombophlebitis of the infused vein in one subject. In conclusion, the 16.5 .mu.g/kg/h infusion rate reliably

achieves plasma factor VII activity levels of 10 IU/mL, but this level does not provide reliable hemostasis.
ST factor VIIa hemostatic surgery
IT Hemostatics
Human
Surgery
(elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII)
IT 102786-61-8, NovoSeven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII)
IT 9001-25-6, Blood-coagulation factor VII
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII)
IT 9001-27-8, Blood coagulation factor VIII
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII)
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REFERENCE 9

AN 136:63854 CA
TI Acquired haemophilia: Experiences with a standardized approach
AU Grunewald, M.; Beneke, H.; Guthner, C.; Germowitz, A.; Brommer, A.; Griesshammer, M.
CS Department of Haematology and Oncology, Haemostaseology Division, University of Ulm, Germany

09921880

SO Haemophilia (2001), 7(2), 164-169
CODEN: HAEMF4; ISSN: 1351-8216
PB Blackwell Science Ltd.
DT Journal
LA English
CC 1-8 (Pharmacology)
Section cross-reference(s): 2
AB Acquired hemophilia is a rare, life-threatening, acquired bleeding diathesis. No general consensus exists on the best therapeutic approach. The authors report on the standardized approach at the authors' institution evaluated in ten patients with acquired hemophilia. Factor VIII inhibitors were found in all patients, activities ranging from 1 to 648 Bethesda units (BU). Eight of the ten patients presented with severe bleeding. Two patients died during the acute phase, one from intracranial bleeding and one due to Mycoplasma pneumonia. One patient with mild bleeding was treated with immunosuppression alone. Two patients with factor VIII inhibitor activities below 5 BU were started on factor VIII conc. therapy. Therapy was successful in one and was changed to recombinant human activated factor VII infusion (rFVIIa) in the other, owing to insufficient factor VIII recovery. Six patients with factor VIII inhibitor activities above 5 BU were started on activated prothrombin complex conc. (APCC) therapy. APCC treatment was successful initially in all six patients and was changed to rFVIIa infusion in one for rebleeding. One patient did not receive any specific therapy. Immunosuppression with prednisolone (2 mg kg-1) was begun in nine patients and was continued with cyclophosphamide (2 mg kg-1) in six. A complete remission of the acquired hemophilia was found in seven of the eight patients surviving the acute phase, one had a partial remission. All patients with acquired hemophilia could be managed effectively following the authors' standardized approach. Routine administration of immunosuppression was assocd. with high inhibitor elimination rates.
ST acquired hemophilia blood coagulation factor immunosuppression
IT Hemophilia
(acquired; standardized treatment of acquired hemophilia in humans)
IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation factor inhibitors; standardized treatment of acquired hemophilia in humans)
IT Hemostatics
Immunosuppressants
(standardized treatment of acquired hemophilia in humans)
IT Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(standardized treatment of acquired hemophilia in humans)
IT 50-18-0, Cyclophosphamide 50-24-8, Prednisolone 9001-26-7, Prothrombin 9001-27-8, Factor VIII 78690-39-8, FEIBA 102786-61-8, NovoSeven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(standardized treatment of acquired hemophilia in humans)
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AN 136:48238 CA
TI Cost-utility analysis of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX
AU Ekert, H.; Brewin, T.; Boey, W.; Davey, P.; Tilden, D.
CS Haemophilia Treatment Centre, Royal Children's Hospital, Parkville, 3052, Australia
SO Haemophilia (2001), 7(3), 279-285
CODEN: HAEMF4; ISSN: 1351-8216
PB Blackwell Science Ltd.
DT Journal
LA English
CC 1-8 (Pharmacology)
AB The high cost of treating patients with inhibitors in an environment of restricted budgets warrants consideration of cost-effectiveness. We detd. the clin. response, effect on quality of life and the cost-effectiveness of treatment with rFVIIa in six boys with long-standing inhibitors to factors VIII or IX, compared with other treatment regimes previously used in these patients. The study used a longitudinal before-and-after design and was conducted in three phases. Phase 1 was 6 mo preceding the introduction of rFVIIa, during which patients received on-demand "usual care" with other treatment regimes; phase 2 was 6 mo treatment on rFVIIa assessed retrospectively; and phase 3 was 6 mo on rfVIIa treatment assessed prospectively. Treatment with rFVIIa was reserved for intraarticular, compartment, psoas, mucosal and suspected intracranial bleeding. Treatment outcomes were obtained by interview using structured questionnaires, the quality-of-life instruments CHQ CF-80 and CHQ PF-50, patient self-reporting diary, interrogation of hospital records, and the EuroQoL EQ-5D for utility valuations. Our results confirm that rFVIIa is clin. effective and resulted in 63-92% redns. in the no. of re-treatments, duration of painful episodes, delay to initiation of treatment, days requiring wheelchair or crutches, emergency room visits and lost carer time compared with the patients' other therapies. Quality-of-life improvements were obsd. in several important areas as perceived by both patients and their families, at an incremental cost per QALY of A $51 533.
ST NovoSeven factor VIIa hemostatic hemophilia child

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IT Hemophilia
(A; cost-utility anal. of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX)
IT Hemophilia
(B; cost-utility anal. of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX)
IT Development, mammalian postnatal
(child; cost-utility anal. of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX)
IT Hemostatics
Human
(cost-utility anal. of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX)
IT 102786-61-8, NovoSeven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cost-utility anal. of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX)
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
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=> s l1 and (specific (W) activity)
72848 SPECIFIC
271 ACTIVITY
0 SPECIFIC (W) ACTIVITY
L2 0 L1 AND (SPECIFIC (W) ACTIVITY)

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=> s novoseven
L3 663 NOVOSEVEN

=> s l3 and (specific (w) activity)
L4 0 L3 AND (SPECIFIC (W) ACTIVITY)

=> s l3 and ((u/mg) or (units/mg))
'MG' IS NOT A VALID FIELD CODE
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'MG' IS NOT A VALID FIELD CODE
L5 0 L3 AND ((U/MG) OR (UNITS/MG))

=> s l3 and ((u or units) (w) mg)
L6 0 L3 AND ((U OR UNITS) (W) MG)

=> s l3 and amidolytic
L7 0 L3 AND AMIDOLYTIC

=> s l3 and protease
L8 7 L3 AND PROTEASE

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 2 DUP REM L8 (5 DUPLICATES REMOVED)

=> d l9 1-2 au so ti py ab

L9 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AU Hoffman, Maureane (1); Monroe, Dougald M., III
SO Seminars in Hematology, (October, 2001) Vol. 38, No. 4 Suppl 12, pp. 6-9. print.
ISSN: 0037-1963.
TI The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis.
PY 2001

L9 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AU Hoffman M; Monroe D M 3rd; Roberts H R
SO BLOOD COAGULATION AND FIBRINOLYSIS, (1998 Mar) 9 Suppl 1 S61-5. Ref: 13

09921880

Journal code: 9102551. ISSN: 0957-5235.

TI Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII.

PY 1998

AB High levels of recombinant activated factor VII (rFVIIa; **NovoSeven** , Novo Nordisk, Bagsvaerd, Denmark) have been found to be effective in providing haemostasis in haemophiliacs and in normal individuals with acquired inhibitors to factor VIII (FVIII) or FIX. However, the mechanism of this therapeutic effect of FVIIa is unclear. Opinion is divided over whether high-dose FVIIa therapy works primarily by a tissue factor (TF)-dependent or -independent mechanism. Our group originally favoured a TF-dependent mechanism; however, we have recently found that, at levels comparable with those attained therapeutically, FVIIa activates enough FX on activated platelets to restore platelet surface thrombin generation. These data now lead us to favour a primarily (although not necessarily exclusively) TF-independent mechanism for the haemostatic effect of high-dose FVIIa. We believe that a platelet surface localization of FVIIa activity explains both its safety and efficacy, as well as its haemostatic effect in patients with thrombocytopenia and platelet function defects. Localization on activated platelets would tend to restrict the activity of FVIIa to sites of injury. Activation of FX on the platelet surface in haemophiliacs would provide FXa in a favourable location to escape inhibition by plasma **protease** inhibitors and be incorporated into platelet prothrombinase complexes. Activation of FIX and FX on platelet surfaces in thrombocytopenia would result in more thrombin generation per platelet, possibly leading to formation of a stable fibrin network even in the absence of an optimal initial platelet plug.

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 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03  JAPIO has been reloaded and enhanced
 NEWS 24  Sep 16  Experimental properties added to the REGISTRY file
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=> s haemtech or haemtechologic
L1            0 HAEMTECH OR HAEMTECHOLOGIC

=> s (factor (w) VII) and (specific (W) activity)
L2          159 (FACTOR (W) VII) AND (SPECIFIC (W) ACTIVITY)

=> s (factor (w) VII) near (specific (W) activity)
MISSING OPERATOR VII) NEAR
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> h
H IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> help commands
Enter one of these commands at the arrow prompt (=>).

ACTIVATE ----- Assign L#s to saved query or answer set.
ANALYZE ------ Build expand terms from answer fields.
ARCHIVE ------ Purchase rights for archiving.
DELETE ------- Delete saved or current session items.
DISPLAY ------ Display saved or current session items.
DUPLICATE ---- Determine duplicate answers
EDIT --------- Modify the text of an E-number entry.
EXPAND ------- Look at the index around a term.
FILE --------- Specify the search and display file.
FOCUS -------- Rank answers in order of relevancy.
FSEARCH ------ Find records from given patent family(s)
FSORT -------- Sort patent records by patent family
HELP --------- For help on how to use the system.
INDEX -------- Specify the Index environment.
LOGOFF ------- End the online session.
NEWS --------- Display current news about the system.
PRINT -------- Print answers offline.
REDISTRIBUTE - Purchase rights for redistribution.
SAVE --------- Save an L-numbered query or answer set.
SDI ---------- Request searches be run on file updates.
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SEARCH ------- Perform a search.
SELECT ------- Build expand terms from answer fields.
SET ---------- Set terminal and interaction options.
SORT --------- Sort Answers of an L-number list
TABULATE ----- Analyze SmartSELECT L-number data.
TRANSFER ----- Extract terms from answers and search.
? ------------ The same as HELP.
Enter one of these commands at the arrow prompt (=>).


For more detailed information about a command, enter HELP followed by
the command name at an arrow prompt.

Example: => HELP SEARCH

For information on entering multiple commands at a single arrow
prompt, enter HELP COMMAND STACKING.

=> search
ENTER LOGIC EXPRESSION, QUERY NAME, OR (END):s
   3 FILES SEARCHED...
L3     9741695 S

=> s l2 and (purified or purification)
L4          79 L2 AND (PURIFIED OR PURIFICATION)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5          46 DUP REM L4 (33 DUPLICATES REMOVED)

=> s l5 and py<=1999
   1 FILES SEARCHED...
   4 FILES SEARCHED...
L6          46 L5 AND PY<=1999

=> d hist

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     FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE, SCISEARCH' ENTERED AT 10:39:58 ON
     18 SEP 2002
L1           0 S HAEMTECH OR HAEMTECHOLOGIC
L2         159 S (FACTOR (W) VII) AND (SPECIFIC (W) ACTIVITY)
L3     9741695 SEARCH S
L4          79 S L2 AND (PURIFIED OR PURIFICATION)
L5          46 DUP REM L4 (33 DUPLICATES REMOVED)
L6          46 S L5 AND PY<=1999

=> d 1-46 l6 pd ti so ab au

L6   ANSWER 1 OF 46  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD   1996
TI   Factor VII binding to tissue factor in plasma from
     warfarin-treated individuals.
SO   Thrombosis Research, (1996) Vol. 81, No. 6, pp. 657-663.
     ISSN: 0049-3848.
AB   Using enzyme immunoassay, we measured the binding ability of artificial
     gamma-carboxyglutamic acid (Gla)-domainless-Factor VII
     (FVII) to tissue factor (TF) or of Factor VII in 44
     patients stabilized by long term treatment with warfarin. Purified
     FVII digested with cathepsin G, that is Gla-domainless-FVII, showed a
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rapid loss in the binding ability of FVIl to TF (FVII-TF binding). After adsorption with Al(OH)-3 of plasma from 8 out of 44 warfarin-treated patients, no FVII clotting activity (FVII:c) was detected in the supernatant, whereas FVII antigen (FVII:ag) and FVII-TF binding remained 19.2% and 17%, respectively, as compared with those before adsorption. In the plasma from 44 warfarin-treated patients the FVII:c (mean +- SD, 54.26 +- 12.50%) was significantly lower than the FVII:ag (77.15 +- 18.24%) (P lt 0.001), although the FVII:c was significantly correlated with FVII:ag (r=0.628). FVII-TF binding (68.27 +- 21.16%) was significantly higher than FVII:c (p lt 0.001), but not than FVII:ag (p gt 0.05). The FVII-TF binding was significantly correlated with FVII:ag (r=0.738), but somewhat poorly with FVII:c (r=0.415). These results show that artificial Gla-domainless-FVII digested with cathepsin C; loses both the clotting activity and the binding ability to TF. However, PIVKA-VII has little or no clotting activity but the binding ability to TF. This suggested that the low **specific activity** of FVII (FVII:c/FVII:ag) in the plasma of warfarin-treated patients would not entirely depend on the decreased FVII-TF binding.

AU Takamiya, Osamu (1); Yoshioka, Akira

L6 ANSWER 2 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

PD 1990

TI RECOMBINANT HUMAN EXTRINSIC PATHWAY INHIBITOR PRODUCTION ISOLATION AND CHARACTERIZATION OF ITS INHIBITORY ACTIVITY ON TISSUE FACTOR-INITIATED COAGULATION REACTIONS.

SO J BIOL CHEM, (1990) 265 (28), 16786-16793.
CODEN: JBCHA3. ISSN: 0021-9258.

AB Previous studies have shown that extrinisic pathway inhibitor (EPI) is an effective inhibitor of factor Xa alone or factor VIIa-tissue factor complex in the presence of factor Xa. Since tissue factor exposure is implicated in thrombogenesis, we hypothesized that EPI may be valuable in the treatment of some thromboembolic episodes. Furthermore, EPI may be an important factor in bleeding complications in hemophiliacs. In the present study, human EPI was expressed in baby hamster kidney cells using a mammalian expression vector. Transfected cells expressed 1-2 .mu.g/ml of recombinant EPI (rEPI) which was **purified** to homogeneity by heparin-Sepharose chromatography, ion-exchange chromatography, and reverse phase high performance liquid chromatography. **Purified** rEPI exhibited a **specific activity** of 30,000 units/mg and migrated as a single band in sodium dodecyl sulfate-polyacrylamide gel electrophoresis with an apparent molecular weight of 42,000. In addition, the NH2-terminal sequence of rEPI was identical to that of HepG2 EPI and HeLa EPI. The ability of rEPI to inhibit factor X activation by a complex of factor VIIa-tissue factor was then examined in the presence and absence of plasma concentrations of human factors VIII and IX. Using relipidated human brain tissue factor apoprotein, rEPI inhibited the factor VIIa-mediated activation of factor X half-maximally at 2.5 and 1 nM in the presence and absence of factors VIII and IX, respectively. Using monolayers of a human bladder carcinoma cell line (J82) as the source of tissue factor, the activation of factor X by cell-bound factor VIIa was inhibited half-maximally by 5 nM rEPI in the presence of factors VIII and IX, and at 0.8 nM EPI in the absence of factors VIII and IX. The proteolytic activity of J82 cell-bound factor Xa toward prothrombin was inhibited half-maximally at .apprx.-5 nM rEPI, while the amidolytic activity of factor Xa in solution was inhibited by rEPI with a Ki of 130 pM. Recombinant EPI also inhibited the amidolytic activity of factor VIIa half-maximally at 10 nM rEPI in the presence of relipidated tissue factor apoprotein and calcium. These results indicate that, in the presence of plasma concentrations of factors VIII and IX, at least 10 times the plasma concentration of EPI is required to reduce factor VIIa-dependent factor X activation one order of magnitude in vitro. In the absence of functional

factor VIII and IX, rEPI at plasma levels was a potent inhibitor of factor VIIa-mediated factor X activation, and this activity presumably accounts for the inability of hemophiliacs to initiate hemostasis via the extrinisic pathway.

AU PEDERSEN A H; NORDFANG O; NORRIS F; WIBERG F C; CHRISTENSEN P M; MOELLER K B; MEIDAHL-PEDERSEN J; BECK T C; NORRIS K; ET AL

L6 ANSWER 3 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1990
TI CANCER PROCOAGULANT IN ACUTE LYMPHOBLASTIC LEUKEMIA.
SO EUR J HAEMATOL, (1990) 45 (2), 78-81.
CODEN: EJHAEC. ISSN: 0902-4441.

AB In a previous study we characterized cancer procoagulant (CP), a 68 kd cysteine proteinase which directly activates coagulation factor X in various subtypes (from M1 to M5) of acute non-lymphoblastic leukemia (ANLL). The aim of this study was to determine whether CP is also expressed by acute lymphoblastic leukemia (ALL) cells. Blasts from 25 ALL patients were extracted and tested for their procoagulant properties. 16 samples (64%) shortened the recalcification time of normal human plasma, and 9 (36%) did not. 8 of the 16 active samples showed properties compatible with CP, i.e. independence from **factor VII** in triggering blood coagulation and sensitivity to cysteine proteinase inhibitors. Selected samples also cross-reacted with a polyclonal antibody raised against **purified** CP. The **specific activity** of CP in ALL extracts was significantly lower than in most ANLL types previously studied (all but M4). These finding indicate that CP can be a property of the lymphoid phenotype although its expression may be lower than in the myeloid phenotype.

AU ALESSIO M G; FALANGA A; CONSONNI R; BASSAN R; MINETTI B; DONATI M B; BARBUI T

L6 ANSWER 4 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1990
TI SYNTHESIS **PURIFICATION** AND CHARACTERIZATION OF AN ARG-152-GLU SITE-DIRECTED MUTANT OF RECOMBINANT HUMAN BLOOD CLOTTING **FACTOR VII**.
SO BIOCHEMISTRY, (1990) 29 (13), 3413-3420.
CODEN: BICHAW. ISSN: 0006-2960.

AB Coagulation **factor VII** circulates in blood as a single-chain zymogen of a serine protease and is converted to its activated two-chain form, factor VIIa, by cleavage of an internal peptide bond located at Arg152-Ile153. Previous studies using serine protease active-site inhibitors suggest that zymogen **factor VII** may possess sufficient proteolytic activity to initiate the extrinsic pathway of blood coagulation. In order to assess the putative intrinsic proteolytic activity of single-chain **factor VII**, we have constructed a site-specific mutant of recombinant human **factor VII** in which arginine-1523 has been replaced with a glutamic acid residue. Mutant **factor VII** was **purified** in a single step from culture supernatants of baby hamster kidney cells transfected with a plasmid containing the sequence for Arg152 .fwdarw. Glu **factor VII** using a calcium-dependent, murine anti-**factor VII** monoclonal antibody column. **Purified** mutant **factor VII** was indistinguishable from plasma-derived or recombinant wild-type **factor VII** by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and migrated as a single band with an apparent molecular weight of 50,000. The average **specific activity** of several mutant **factor VII** preparations was 0.00025 unit/.mu.g, or 0.01% of that observed for recombinant wild-type factor **factor VII** preparations. The clotting activity of mutant

factor VII was, however, completely inhibited following incubation with dansyl-Glu-Gly-Arg chloromethyl ketone, suggesting that the apparent clotting activity of mutant **factor VII** was due to a contaminating serine protease. Immunoblots of mutants **factor VII** incubated with human factor IXa revealed no cleavage, whereas incubation of mutant **factor VII** with human factor Xa resulted in cleavage of mutant **factor VII** and the formation of a lower molecular weight degradation product migrating at Mr .apprxeq. 40,000. Incubation of mutant **factor VII** with Staphylococcus aureus V8 protease resulted in the proteolytic activation of mutants **factor VII** followed by a progressive decline in activity as a result of proteolytic degradation. By comparison, incubation of recombinant wild-type **factor VII** with V8 protease resulted in the proteolytic degradation of **factor VII** and loss of coagulant activity without an apparent transient increase in activity. Our results are consistent with the proposal that zymogen **factor VII** possesses no intrinsic proteolytic activityy toward factor X or Factor IX.

AU WILDGOOSE P; BERKNER K L; KISIEL W

L6 ANSWER 5 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1988
TI RESOLUTION OF MONOMERIC AND HETERODIMERIC FORMS OF TISSUE FACTOR THE HIGH-AFFINITY CELLULAR RECEPTOR FOR **FACTOR VII**.
SO THROMB RES, (1988) 50 (4), 481-494.
CODEN: THBRAA. ISSN: 0049-3848.
AB Tissue factor (TF) is the high affinity cell surface receptor and obligatory cofactor for plasma coagulation **factor VII**. **Purification** of TF from human brain and placenta has recently been reported to yield both a monomeric 47 kDa protein as well as a 58 kDa heterodimeric form. In this study, the TF glycoprotein was isolated from human brain by immunoaffinity chromatography using a newly developed monoclonal antibody, TF8-5G9, and was compared to TF isolated by **factor VII**-affinity chromatography. Except for the greater efficiency of the immunoaffinity method, both methods yielded TF with similar **specific activities**, and both preparations contained the monomeric and heterodimeric forms of TF. The 58 kDa form was established to be a disulfide-linked heterodimer composed of TF and the alpha chain of hemoglobin. From these results and from studies of immunoprecipitation of TF from cultured fibroblast cells, we conclude that the 47 kDa monomeric form of TF is the naturally occurring cellular form of TF, and that heterodimer formation is a secondary event. The potential significance of the proclivity of TF to form a heterodimer with hemoglobin is discussed.
AU MORRISSEY J H; REVAK D; TEJADA P; FAIR D S; EDGINGTON T S

L6 ANSWER 6 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1987
TI AFFINITY **PURIFICATION** OF HUMAN BRAIN TISSUE FACTOR UTILIZING **FACTOR VII** BOUND TO IMMOBILIZED ANTI-**FACTOR VII**.
SO ANAL BIOCHEM, (1987) 165 (2), 365-370.
CODEN: ANBCA2. ISSN: 0003-2697.
AB An efficient procedure for affinity **purification** of human tissue factor apoprotein that requires binding of only microgram quantities of human **factor VII** to anti-**factor VII** agarose is described. **Factor VII** was added to a 2% Triton X-100 extract of acetone brain powder in the presence of calcium. The resultant **factor VII**/tissue factor-calcium complex was found to anti-**factor VII**-agarose, and the bound

tissue factor was then eluted with EDTA. The eluate was passed through anti-goat IgG-agarose to remove contaminating goat IgG that leaks from the anti-**factor VII** column. Yield (units of activity) was 27%; **specific activity** was 2400 U/mg, which corresponds to that reported by others. The **purified** apoprotein migrated as a single band on sodium dodecyl sulfate-polyacrylamide gel electrophoresis with an apparent molecular weight of 47,000. Immunostaining with a goat anti-tissue factor IgG raised against the **purified** material yielded a major band of the same apparent molecular weight. **Factor VII** remains bound to the column and, therefore, for subsequent use preincubation of tissue factor with **factor VII** and calcium is not required. Thus, the present purificaiton procedure markedly reduces the amount of **factor VII** needed as affinity ligand to purify tissue factor apoprotein.

AU RAO L V M; RAPAPORT S I

L6 ANSWER 7 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1987
TI ISOLATION OF THE TISSUE FACTOR INHIBITOR PRODUCED BY HEP-G2 HEPATOMA CELLS.
SO PROC NATL ACAD SCI U S A, (1987) 84 (7), 1886-1890.
CODEN: PNASA6. ISSN: 0027-8424.
AB Progressive inhibition of tissue factor activity occurs upon its addition to human plasma (serum). This process requires the presence of **factor VII**(a), factor X(a), Ca2+, and another component in plasma that we have called the tissue factor inhibitor (TFI). A TFI secreted by HepG2 cells (human hepatoma cell line) was isolated from a serum-free conditioned medium in a four-step procedure including CdCl2 precipitation, diisopropylphosphoryl-factor Xa affinity chromatography, Sephadex G-75 superfine in gel filtration, and Mono Q ion-exchange chromatography the **purified** TFI contained a predominant band at Mr 38,000 on NaDodSO4/polyacrylamide gel electrophoresis that comigrates with inhibitory activity. Like the activity present in plasma, this TFI requires that presence of **factor VII**(a), factor X(a), and Ca2+ to express inhibitory activity. Its **specific activity** (assuming on extinction coeficient of 10 at 280 nM, for a 1-cm path length through a 1% solution) was 9800 units/mg of protein, where 1 unit of TFI activity was defined as that present in 1 ml of normal pooled serum.
AU BROZE G J JR; MILETICH J P

L6 ANSWER 8 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD **1986 (RECD 1987)**
TI CHARACTERIZATION OF FOUR MONOCLONAL ANTIBODIES TO **FACTOR VII** COAGULANT PROTEIN AND THEIR USE IN IMMUNOPURIFICATION OF FACTOR VIII.
SO THROMB HAEMOSTASIS, (**1986 (RECD 1987)**) 56 (3), 271-276.
CODEN: THHADQ. ISSN: 0340-6245.
AB Four monoclonal anti-VIII:C antibodies were obtained from the fusion of the splenocytes of one Balb/C mouse with a **specific activity** ranging from 2.3 to 45,000 U/mg when **purified** from ascitic fluid. Only one antibody was able to inhibit completely Factor VIII:C in normal plasma. The four antibodies could bind Factor VIII:CAg in plasma and commercial concentrated both in liquid and solid phase, and were suitable for immunopurification of Factor VIII:C. Three antibodies competed with polyclonal anti-VIII:CAg Fab' in a liquid phase IRMA, and all of them were able to displace their own binding to Factor VIII:CAg. Competition studies between monoclonal antibodies for the binding to Factor VIII:CAg were performed and showed the recognition of different epitopes and various functional impact. These studies indicate

that at least one antibody, with the lowest anti-VIII:C titer clearly recognizes a different epitope of VIII:C than those recognized by the others. Affinity constants ranged from 109 to 1010 l/mole.
AU CROISSANT M-P; VAN DE POL H; LEE H H; ALLAIN J-P

L6 ANSWER 9 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1985
TI TISSUE FACTOR IN BRONCHOALVEOLAR LAVAGE FLUIDS EVIDENCE FOR AN ALVEOLAR MACROPHAGE SOURCE.
SO AM REV RESPIR DIS, (1985) 131 (3), 331-336.
CODEN: ARDSBL. ISSN: 0003-0805.
AB Local and systemic coagulation and fibrin deposition occur in many types of alveolar injury and inflammation, but clotting factors capable of initiating the coagulation cascade in the alveolus were not thoroughly identified and characterized. BAL (bronchoalveolar lavage) fluids obtained from rabbits had procoagulant activity detectable in dilutions containing as little as 1.3 ng of protein. The **specific activity** of the procoagulant in these fluids was within 1 order of magnitude of that found in brain thromboplastin. The BAL procoagulant was shown to be associated with particles having a MW greater than 15 .times. 106 daltons by gel filtration chromatography, and was characterized as tissue factor by showing specific requirements for **factors VII**, X and II. Further experiments were performed using membranes **purified** from alveolar macrophages by sucrose density gradients and characterized by studies of alkaline phosphodiesterase I, a cytoplasmic membrane marker, and EM. Alveolar macrophages, especially low-density subpopulations, generate and release membrane material that is a source of tissue factor in BAL fluids.
AU MCGEE M P; ROTHBERGER H

L6 ANSWER 10 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1984
TI COAGULATION FACTOR-IX CONCENTRATE METHOD OF PREPARATION AND ASSESSMENT OF POTENTIAL IN-VIVO THROMBOGENICITY IN ANIMAL MODELS.
SO BLOOD, (1984) 64 (6), 1220-1227.
CODEN: BLOOAW. ISSN: 0006-4971.
AB Thrombosis and/or disseminated intravascular coagulation (DIC) are complications specifically associated with the use of factor IX complex in some patients. Assuming that these complications might result from zymogen overload, a factor IX concentrate (coagulation factor IX) was produced using diethylaminoethyl (DEAE)-Sephadex and sulfated dextran chromatography, that is essentially free of prothrombin, **factor VII** and factor X. Factor IX **specific activity** is at least 5 U/mg protein, a 250-fold **purification** compared to plasma. Amounts of factors II, VII and X are less than 5 U each per 100 U of factor IX. The concentrate is essentially free of activated clotting factors and contains no added heparin. In the rabbit stasis model, a dose of 200 factor IX U/kg was less thrombogenic than 100 factor IX U/kg of the DEAE-Sephadex eluate from which the concentrate was derived. Infusion of 200 factor IX U/kg did not induce DIC in the nonstasis rabbit model, whereas 100 factor IX U/kg of the DEAE-Sephadex eluate resulted in DIC in this model. Several factor IX lots were found to have shortened nonactivated partial thromboplastin times (PTT), but were nonthrombogenic in both animal models. Coagulation factor IX concentrate apparently is less thrombogenic than factor IX complex.
AU MENACHE D; BEHRE H E; ORTHNER C L; NUNEZ H; ANDERSON H D; TRIANTAPHYLLOPOULOS D C; KOSOW D P

L6 ANSWER 11 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1983
TI QUANTITATION OF **FACTOR VII** IN THE PLASMA OF NORMAL AND

09921880

WARFARIN TREATED INDIVIDUALS BY RADIO IMMUNOASSAY.
SO BLOOD, (1983) 62 (4), 784-791.
CODEN: BLOOAW. ISSN: 0006-4971.
AB Highly **purified** single-chain **factor VII** was isolated from plasma and used to generate monospecific antibodies. A double-antibody equilibrium radioimmunoassay was constructed. The assay was tested for and met all the criteria required for a specific, sensitive and accurate determination of **factor VII** in plasma. The range of sensitivity of the assay was between 1 and 500 ng **factor VII**/ml, and the coefficient of variation was 1-3% within assay and 12-16% between assays. Pure **factor VII** and plasmic **factor VII** from normal, warfarin-treated and hereditary deficient individuals inhibited competition assays with parallel slopes, indicating the expression of similar epitopes by these molecules and validating the measurement of this protein in plasma. The concentration of **factor VII** normal plasma (n = 41) was 470 .+-. 112 ng/ml, and the measurement of **factor VII** antigen correlated with activity (r = 0.82). **Factor VII** concentration in the plasma of individuals on warfarin therapy (n = 24) was 238 .+-. 73 ng/ml. **Factor VII** activity was .apprx. 38% of normal and correlated less well with **factor VII** antigen (r = 0.53). The **specific activity** of these molecules was 78% of normal (P < 0.01), suggesting the presence of nonfunctional or partially functional molecules in the circulation of individuals undergoing drug therapy. Analysis of 2 hereditary deficicent patients revealed that, while there were significant levels of **factor VII** protein, the procoagulant activity was < 2%, indicating a discordant relationship of these parameters in individuals expressing the deficient **factor VII** phenotype.
AU FAIR D S

L6 ANSWER 12 OF 46 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
PD 1981
TI ISOLATION AND CHARACTERIZATION OF HUMAN **FACTOR-VII** ACTIVATION OF **FACTOR VII** BY FACTOR-XA.
SO J BIOL CHEM, (1981) 256 (1), 253-259.
CODEN: JBCHA3. ISSN: 0021-9258.
AB A procedure was developed for the isolation of human **factor VII** to apparent homogeneity as judged by the analytical disc electrophoretic system of Davis (pH 8.9) and by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis [PAGE]. The isolation procedure involves adsorption of **factor VII** onto barium citrate, ammonium sulfate fractionation, DEAE-Sephadex chromatography and preparative PAGE. The overall yield of **factor VII** is 15-20% of starting plasma, and the **purified** protein has a **specific activity** of 1800-2200 U/mg in a clotting assay. **Factor VII** protein obtained by this method has only 1.3-1.5 times more activity in a 1-stage clotting assay than in a coupled amidolytic assay, which is taken to mean that it contains less than 5% of activated **factor VII**. Human **factor VII** is a single chain glycoprotein with an apparent MW of 50,000 .+-. 2,000 as determined by SDS-PAGE. It has alanine as an NH2-terminal amino acid residue and contains 8.8 .gamma.-carboxyglutamic acid residues/mol of protein. Incubation of **purified factor VII** with factor Xa in the presence of Ca(II) and phospholipid results in a rapid up to 25-fold increase in its clotting activity. **Factor VII** activity in the coupled amidolytic assay remains unchanged throughout the incubation. Activation of **factor VII** by factor Xa is associated with cleavage of the MW = 50,000 native protein to a protein consisting of 2 chains of MW = about 26,000 and 22,000, as determined by SDS-PAGE in the presence of

2-mercaptoethanol. Other properties of human **factor VII**, including its amino acid composition and its reactions with an anti-**factor VII** antibody, are described.

AU BAJAJ S P; RAPAPORT S I; BROWN S F

L6 ANSWER 13 OF 46 MEDLINE

TI Factor VIIa/tissue factor generates a form of factor V with unchanged **specific activity**, resistance to activation by thrombin, and increased sensitivity to activated protein C.

SO BIOCHEMISTRY, **(1999 Feb 9)** 38 (6) 1829-37.
Journal code: 0370623. ISSN: 0006-2960.

AB Factor VIIa, in complex with tissue factor (TF), is the serine protease responsible for initiating the clotting cascade. This enzyme complex (TF/VIIa) has extremely restricted substrate specificity, recognizing only three previously known macromolecular substrates (serine protease zymogens, **factors VII**, IX, and X). In this study, we found that TF/VIIa was able to cleave multiple peptide bonds in the coagulation cofactor, factor V. SDS-PAGE analysis and sequencing indicated the factor V was cleaved at Arg679, Arg709, Arg1018, and Arg1192, resulting in a molecule with a truncated heavy chain and an extended light chain. This product (FVTF/VIIa) had essentially unchanged activity in clotting assays when compared to the starting material. TF reconstituted into phosphatidylcholine vesicles was ineffective as a cofactor for the factor VIIa cleavage of factor V. However, incorporation of phosphatidylethanolamine in the vesicles had little effect over the presence of 20% phosphatidylserine. FVTF/VIIa was as sensitive to inactivation by activated protein C (APC) as thrombin activated factor V as measured in clotting assays or by the appearance of the expected heavy chain cleavage products. The FVTF/VIIa could be further cleaved by thrombin to release the normal light chain, albeit at a significantly slower rate than native factor V, to yield a fully functional product. These studies thus reveal an additional substrate for the TF/VIIa complex. They also indicate a new potential regulatory pathway of the coagulation cascade, i.e., the production of a form of factor V that can be destroyed by APC without the requirement for full activation of the cofactor precursor.

AU Safa O; Morrissey J H; Esmon C T; Esmon N L

L6 ANSWER 14 OF 46 MEDLINE

TI In vitro characterization of high purity factor IX concentrates for the treatment of hemophilia B.

SO THROMBOSIS AND HAEMOSTASIS, **(1995 Apr)** 73 (4) 584-91.
Journal code: 7608063. ISSN: 0340-6245.

AB This study employed sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis and immunoblotting to assess the purity of seven high purity factor IX concentrates: Aimafix (Aima), AlphaNine-SD (Alpha Therapeutic), Factor IX VHP (Biotransfusion), Immunine (Immuno), Mononine (Armour Pharmaceutical), Nanotiv (Kabi Pharmacia), and 9MC (Blood Products Laboratory). The mean **specific activity** of these products ranged from 68 U factor IX/mg (Aimafix) to 246 U factor IX/mg (Mononine). SDS-PAGE analysis showed that the highest purity product, Mononine, had a single contaminating band under non-reducing conditions. Two additional bands were detected when this product was analyzed under reducing conditions. All other products had multiple contaminating bands that were more apparent under reducing than non-reducing conditions. The immunoblot for factor IX showed a dominant factor IX band for all products. In addition, visible light chain of factor IX was detected for AlphaNine-SD, Factor IX VHP, Immunine, Mononine, Nanotiv, and 9MC, suggesting that the factor IX in these products had undergone partial activation to factor IXa. Another contaminating band was visible at 49,500 for all of the products except

9MC. In addition to this band, high molecular weight contaminants were apparent for some products, most notably AlphaNine-SD. The identity of these bands is unknown. Immunoblotting failed to demonstrate **factor VII** as a contaminant of any of the high purity products, although factor VIIa could be detected in some lots of Immunine, Nanotiv, and 9MC by a clot-based assay. Factor X contaminated Aimafix, AlphaNine-SD, Factor IX VHP, Immunine, Nanotiv, and 9MC, but activation products of factor X were not detected.(ABSTRACT TRUNCATED AT 250 WORDS)
AU Limentani S A; Gowell K P; Deitcher S R

L6 ANSWER 15 OF 46 MEDLINE
TI Characterization of human tissue factor pathway inhibitor variants expressed in Saccharomyces cerevisiae.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1993 Jun 25)** 268 (18) 13344-51.
Journal code: 2985121R. ISSN: 0021-9258.
AB Human tissue factor pathway inhibitor (TFPI) and three derivatives with deletions of: 1) the complete COOH-terminal third of the polypeptide including the third Kunitz domain, 2) the third Kunitz domain alone, or 3) the penultimate basic COOH-terminal region alone were expressed in yeast as secreted products. High expression yield was obtained only with the derivative that lacked both the third Kunitz domain and the penultimate COOH tail (TFPI1-161). The **purified** short form was heterogeneously glycosylated with a high mannose glycan. The **specific activities** of the different mutant polypeptides toward FXa.tissue factor.FVIIa in a chromogenic assay were similar to that of TFPI expressed in baby hamster kidney cells, suggesting that correct folding takes place in yeast and that neither the third Kunitz domain nor the COOH-terminal region is required for this activity. However, in a clotting assay the anticoagulant activities of yeast-produced TFPI and the shortened derivative TFPI1-161 were about 5- and 50-fold lower, respectively, than for full-length TFPI from mammalian cells. Clotting assays with **purified** short form TFPI showed that it acted mainly via inhibition of FVIIa.tissue factor rather than FXa. The anticoagulant activity of short form TFPI was comparable with that of high affinity antibodies toward tissue factor.
AU Petersen J G; Meyn G; Rasmussen J S; Petersen J; Bjorn S E; Jonassen I; Christiansen L; Nordfang O

L6 ANSWER 16 OF 46 MEDLINE
TI Human coagulation factor IX: assessment of thrombogenicity in animal models and viral safety.
SO JOURNAL OF LABORATORY AND CLINICAL MEDICINE, **(1993 Mar)** 121 (3) 394-405.
Journal code: 0375375. ISSN: 0022-2143.
AB Thromboembolic complications associated with prothrombin complex concentrate treatment may be related to the high levels of factors II and X in these products. We report here results from preclinical safety studies with a human coagulation factor IX product (AlphaNine; Alpha Therapeutic Corp., Los Angeles, Calif.) that contains no detectable factor II or VII and less than 10 units of factor X/100 units of factor IX. This product was manufactured from virally inactivated factor IX complex with a barium citrate adsorption step followed by affinity chromatography yielding factor IX concentrate with a **specific activity** of about 86 factor IX units/mg protein. Electrophoresis and immunoblot analysis indicated that the factor IX represents about 65% of the protein in this product. The virus inactivation step incorporated into the manufacturing process (incubation with n-heptane at 60 degrees C for 20 hours) was shown to inactivate at least 8.6 logs of type 1 human immunodeficiency virus. The barium citrate adsorption and affinity chromatography steps were found to remove 2.0 logs of the marker virus,

vaccinia, and the DEAE ion-exchange chromatography used to produce factor IX complex was found to remove 1.4 logs of the marker virus, Sindbis. Analysis of three separate manufacturing lots with the polymerase chain reaction revealed no evidence of hepatitis C virus. The **purified** factor IX was nonthrombogenic when tested at doses of 450 units/kilogram in a rabbit stasis (Wessler) model, whereas the prothrombin complex concentrates were found to be thrombogenic at doses of less than 50 units/kg. There was no evidence of DIC in a porcine model after infusion of 200 units/kg of coagulation factor IX, as manifested by negative fibrin monomer tests, the absence of fibrin in blood vessels at autopsy, little or no change in prothrombin times and partial thromboplastin times, and only moderate decreases in platelet levels after infusion.

AU Herring S W; Abildgaard C; Shitanishi K T; Harrison J; Gendler S; Heldebrant C M

L6 ANSWER 17 OF 46 MEDLINE

TI **Purification** and properties of heparin-releasable lipoprotein-associated coagulation inhibitor.

SO BLOOD, **(1991 Jul 15)** 78 (2) 394-400.
Journal code: 7603509. ISSN: 0006-4971.

AB The lipoprotein-associated coagulation inhibitor (LACI) is present in vivo in at least three different pools: sequestered in platelets, associated with plasma lipoproteins, and released into plasma by intravenous heparin, possibly from vascular endothelium. In this study we have **purified** the heparin-relesable form of LACI from post-heparin plasma and show that it is structurally different from lipoprotein LACI. The **purification** scheme uses heparin-agarose chromatography, immunoaffinity chromatography, and size-exclusion chromatography and results in a 185,000-fold **purification** with a 33% yield. Heparin-releasable LACI (HRL), as analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, under reducing conditions, appears as a major band at 40 Kd and a minor band at 36 Kd. Immunoblot analysis suggests that the 36-Kd band arises from carboxyl-terminus proteolysis that occurs during the **purification**. HRL has a **specific activity** similar to that of HepG2 or lipoprotein LACI. HRL and lipoprotein LACI combine with lipoproteins in vitro while **purified** HepG2 LACI does not. I125-labeled HRL, injected into a rabbit, is cleared more slowly than I125-labeled HepG2 LACI, which may be due to attachment to lipoproteins in vivo. Preliminary evidence suggests that HRL is associated with vascular endothelium, possibly by attachment to glycosaminoglycans.

AU Novotny W F; Palmier M; Wun T C; Broze G J Jr; Miletich J P

L6 ANSWER 18 OF 46 MEDLINE

TI Immunoaffinity **purification** and characterization of lipoprotein-associated coagulation inhibitors from Hep G2 hepatoma, Chang liver, and SK hepatoma cells. A comparative study.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1990 Sep 25)** 265 (27) 16096-101.
Journal code: 2985121R. ISSN: 0021-9258.

AB A polyclonal antibody against a synthetic peptide corresponding to amino acids 3-25 of mature lipoprotein-associated coagulation inhibitor (LACI) was raised in rabbits. The antibody was used to study the production of LACI by Hep G2 hepatoma, Chang liver, and SK hepatoma cells, and to purify LACI from the culture media. By using an amidolytic assay for factor Xa, it was found that the culture media from these liver-derived cell lines contain inhibitors of factor Xa. In Hep G2 hepatoma culture medium, approximately 50% of Xa inhibitory activity was due to LACI. In the Chang liver and SK hepatoma culture media over 95% of the Xa inhibitory activity was due to LACI. The LACIs were **purified** from these media by immunoaffinity chromatography on an anti-LACI-Ig-Sepharose 4B column and

preparative sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The **purified** LA-CIs varied in molecular weight depending on whether the media were concentrated before chromatography. An Mr approximately 38,000 LACI was obtained by chromatography of unconcentrated media. Chromatography of concentrated media yielded a LACI of Mr approximately 35,000 with the same amino-terminal sequence, suggesting partial proteolysis in the carboxyl-terminal region. In addition, an Mr approximately 25,000 form of LACI was also present. The **purified** Mr approximately 38,000 and approximately 35,000 LACI species from the above cells possess similar **specific activities** when measured by an anti-Xa/amidolysis assay. To study the role of LACI in the control of coagulation, pooled human plasma was depleted of LACI antigen by immunoaffinity absorption and reconstituted with varying amounts of **purified** LACI to examine the effect on tissue factor (TF)-induced coagulation. LACI depletion shortens the time of TF-induced clotting of plasma and the clotting time is linearly related to the LACI concentration after reconstitution. These results suggest that LACI plays an important role in limiting TF-induced coagulation in human plasma. Comparison of the potencies of various **purified** LACIs in the prolongation of TF-induced coagulation revealed that LA-CIs from different sources are not equivalent. The plasma LACI, SK hepatoma LACI, and Chang liver LACI are approximately 7-, 6-7, and 1.3-fold higher in **specific activity** than Hep G2 hepatoma LACI in the TF-induced clotting assay when compared on an anti-Xa/amidolysis unit basis, suggesting possible differences in post-translational modification of these LA-CIs.

AU Wun T C; Huang M D; Kretzmer K K; Palmier M O; Day K C; Bulock J W; Fok K F; Broze G J Jr

L6 ANSWER 19 OF 46 MEDLINE

TI Production of freeze-dried human antihaemophilic cryoprecipitate.

SO JOURNAL OF CLINICAL PATHOLOGY, **(1981 Oct)** 34 (10) 1091-3.
Journal code: 0376601. ISSN: 0021-9746.

AB Concentration of factor VIII from fresh plasma by cryoprecipitation remains the basis for preparation of products used to treat haemophilia A. This paper describes the preparation of a factor VIII concentrate from small plasma pools in transfusion centres with drying facilities. The dried concentrate from one litre of plasma dissolves very well in 50 or 100 ml of distilled water and contains around 500 IU per bottle. The **specific activity** per mg protein is 0.19 IU and the fibrinogen concentration is half that in frozen cryoprecipitate. This method of drying causes no appreciable loss in the factor VIIIC activity and little denaturation as shown by the factor-VIII-related antigen/factor VIIIC ratio of 1.7.

AU Millgan G; Graham R; Hanratty S; Muir W; Mitchell R

L6 ANSWER 20 OF 46 MEDLINE

TI Physical, chemical and immunological studies on bovine factor VIII.

SO HAEMOSTASIS, **(1976)** 5 (1) 1-13.
Journal code: 0371574. ISSN: 0301-0147.

AB Highly **purified** bovine **factor VII** prepared according to our technique and having a **specific activity** of 500 U/mg protein has been studied. The chemical analysis of the preparation revealed it to be composed of amino acids, lipids (8-10%) and carbohydrates (7%). The lipid moiety can be removed by chromatography. Different mechanism of inactivation of bovine **factor VII** and the possible molecular changes induced by the inactivating agents were studied. EDTA and EGTA provoke a weakening of the bonds linking the structural elements of the molecule, which allows for the separation of two different components of the molecule by gel filtration. Upon treatment with thrombin, the carbohydrate content of bovine factor VIII decreases without any apparent degradation of the

protein moiety of the molecule. The fact that precipitating and neutralizing antisera against factor VIII were obtained, shows that the molecules modified by EDTA and thrombin still have the antigenic properties of factor VIII. The inhibitor developed by hemophiliacs transfused with human factor VIII is bound to bovine factor VIII, forming a complex reveal that it is composed of bovine factor VIII and human gamma-globulin. Bovine factor VIII in the complex retains some antigenic determinants which bind rabbit antiserum against bovine factor VIII, as shown by neutralization of the antiserum and by precipitation studies.
AU Casillas G; Simonetti C; Vasquez C; Pavlovsky A

L6 ANSWER 21 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Method for **purification** of blood coagulation factor IX
SO U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 662,927, abandoned.
CODEN: USXXAM
AB A novel method of protecting blood coagulation factor IX from proteases during **purifn.** or storage is disclosed. High concns. of 1 or more water-sol. org. or inorg. salts are used to stabilize factor IX, contained within blood plasma-derived solns., or contained within solns. derived from other sources, against conversion to clin. unacceptable peptide structures such as factor IXa, and/or degraded factor IX peptides. The technique is useful in stabilizing intermediate purity factor IX prepns. during **purifn.**, and in maintaining the integrity of **purified** factor IX during long-term storage. Stable high **specific activity** factor IX prepns. are also disclosed.
A sample of DEAE Sephadex eluate of coagulation factor IX produced contg. 1M NaCl and 10 mM sodium citrate, pH 7.0 was clarified and sterile filtered prior to storage at -80.degree.. Sep. 5-mL aliquots of the thawed soln. were dialyzed overnight at 3.degree. against 1M solns. of NaOAc, LiCl, MgCl2, KCl, NaCl or Na2SO4. LiCl, KCl, NaCl, MgCl2 and Na2SO4 are strongly factor-IX protecting at 1.0M. Such effects can be demonstrated in both certain strongly salting in salts (NaSCN or KSCN) and certain moderately salting out salts (KCl and Na2SO4).
IN Huang, Chin C.; Takashi, Enkoji; Ho, Laura; Kleszynski, Richard R.; Weeks, Richard L.; Feldman, Fred

L6 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Preparation of blood-coagulation **factor VII** for pharmaceutical usage
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
AB The invention relates to a prepn. based on blood clotting **factor VII** with a fraction of less than 5 % of factor VIIa, which exhibits a **specific activity** of at least 50 E/mg and is stable in the absence of blood clotting inhibitors. The invention also relates to a method for producing such a prepn. starting from blood or cell cultures and using anion exchange and hydrophobic chromatog. for **purifn.** The blood-coagulation **factor VII** fraction contains at least one of the following factors: II, IX, or X; further it contains heparin; and it can contain antithrombin III or atheplex. The product is lyophilized and used for infusions.
IN Matthiessen, Peter; Turecek, Peter; Schwarz, Hans-Peter

L6 ANSWER 23 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Process for preparing an activated **factor VII** concentrate having a high purity from human plasma
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
AB Factor VIIa is prepd. from plasma, preferably human plasma, from which cryoppts. have been removed. The plasma is subjected to anion-exchange chromatog. and activation of **factor VII** is

accomplished without addn. of exogenous protein. Factor VIIa essentially free of vitamin K-dependent factors, factor VIIIc, and factor VIIIcAg; in ratio of factor VIIa to **factor VII** of >5; and with a **specific activity** >200 IU/mg protein is produced by this process.

IN Dazey, Bernard; Hamsany, Mohamed; Enfedaque-Morer, Sylvia

L6 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Examining the possible isolation of factor IX complex by ion-exchange column chromatography

SO Khim.-Farm. Zh. (**1991**), 25(6), 59-60
CODEN: KHFZAN; ISSN: 0023-1134

AB The study was undertaken to examine if the TSK gel, DEAE-Toyopearl (Japan) might be used in the chromatog. sepn. of plasma supernatant to prep. a blood coagulation factor IX conc. (FIX C). When applying a linear gradient ionic from 0.15 to 2.0M NaCl, albumin-free FIX C was obtained of a **specific activity** 686.7 units/g protein, as calcd. for Factor IX, which was nearly 50 times as high as that for the starting sample of a plasma cryosupernatant. Stepwise elution allows one to purify FIX C of **factor VII**. Thus, plasma cyrosupernatant sepn. with a DEAE-Toyopearl anion exchanger isolates FIX C from the major plasma proteins, suggesting that the sorbent might be promising for preparative isolation of FIX C.

AU Azigirova, M. A.; Vyazova, E. P.; Shaprova, N. N.; Kheilomskii, A. B.; Zeinalov, A. M.

L6 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Enrichment of blood-coagulation factors II, VII, IX, and X by chromatography

SO Ger., 5 pp.
CODEN: GWXXAW

AB Blood-coagulation factors II, VII, IX, and X are enriched from plasma, plasma fractions, etc. by adsorption on a polymer matrix bearing NH2 and OH groups positioned on a polymer followed by elution. Thus, dild. citrated plasma was passed through a column of glycidyl methacrylate-pentaerythritol dimethacrylate-polyvinyl alc. copolymer equilibrated with 10 mM citrate buffer (pH 7.0); the column was washed with the buffer and eluted with 0.5 M NaCl. The yield of factors II, VII, IX, and X was 60-80%; their **specific activities** were 2.1, 1.9, 2.3, and 2.0 units/mg protein, resp.

IN Kraus, Michael; Moeller, Wolfgang; Eichentopf, Bertram

L6 ANSWER 26 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Concentrates of coagulation factors II, VII, IX and/or X, their preparation and use, and method for the determination of coagulation **factor VII**

SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW

AB Concs. of coagulation factors II, VII, IX, and/or X are prepd. by selective sorption on poly(DEAE-hydroxyethyl acrylate) or poly(DEAE-hydroxyethyl methacrylate)(I) and desorption with a pH 7.2-7.6 buffer contg. 0.3-2.0 mol NaCl/L. Blood-coagulation **factor VII** is detd. in human and animal plasma and in milk, etc., by contacting the sample with a conc. of factors II and X in the presence of thromboplastin, phospholipids, Ca2+, chromogenic substrate [e.g. Z-Gly-Pro-Arg-X (Z = protective group; X = chromophore, e.g. derived from p-nitroaniline, etc.)], and eventually factor V, and detg. the resulting color generated by the liberated thrombin and chromogenic substrate. Human plasma was passed through a column of I equilibrated at pH 7.4 with buffer contg. 3-Na citrate 0.01 and NaCl 0.1M. Undesired proteins were removed with the citrate buffer contg. 0.2M NaCl and then elution was

carried out with a salt gradient of 0.2-0.8M NaCl. Factors IX, II and X and VII were eluted at saline concns. of 0.3-0.4, 0.45-0.55, and 0.7-0.8 M, resp. The **specific activities** of the factor concs. were 40-45, 50-65, and .gtoreq.70 times that in plasma, resp. A conc. of factors II and X was prepd. from bovine blood plasma for use in the detn. of **factor VII** in cattle milk to detect bovine mastitis.

IN Rybak, Miroslav; Kasafirek, Evzen; Houskova, Jitka; Losticky, Cyril; Ulrych, Stanislav; Sedlmaier, Oldrich; Roubalova, Alena

L6 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI A process for isolating coagulation factors, and adsorbent material suitable therefor containing aminoalkylcarbamylalkyl-polymer carriers

SO Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW

AB Blood-coagulation factors are isolated from blood plasma, plasma products, cell lysates, fermn. medium, etc. by liq. chromatog. using an adsorbent comprising a polymeric carrier to which ligands, consisting of primary, secondary, tertiary, or quaternary amino groups, are linked via spacers having .gtoreq.6 atoms and contg. .gtoreq.1 link having hydrophilic properties. The spacers preferably have the formula (CH2)mCONH(CH2)n (m, n = 1-6; m + n .gtoreq.4). Blood plasma was pretreated with DEAE-Sephadex A50 to bind blood-coagulation factors FII, FVII, FIX, and FX. FVIII was then **purified** from the plasma on aminobutylcarbamylbutyl Sepharose CL4B with a yield of 450 U/kg plasma and a **specific activity** of 4.7 U/mg/protein.

IN Riethorst, Waander; Koenig, Boudewijn Wynand; Van Aken, Willem Gerard; Bantjes, Adriaan; Beugeling, Tom; Te Booy, Marcelinus P. W. M.

L6 ANSWER 28 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Preparation of a concentrate of high-purity human factor IX and of other plasma proteins, and their therapeutical use

SO Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW

AB Blood-coagulation factor IX (useful in treating hemorrhages of hemophilia B) is **purified** from human plasma by anion exchange chromatog. followed by affinity chromatog. on immobilized heparin. In the process, other plasma proteins may also be obtained, e.g. .alpha.1-antitrypsin, **factor VII**, etc. Factor IX, with a **specific activity** of 130 IU/mg, was **purified** from cryoppt. supernatant by pretreatment with DEAE-Sephadex A50, chromatog. on DEAE-Sepharose CL-6B in the presence of heparin, and chromatog. on heparin-Sepharose.

IN Burnouf, Thierry; Michalski, Cathérine

L6 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Isolation and characterization of different activated forms of factor VIII, the human antihemophilic A factor

SO Eur. J. Biochem. (**1989**), 185(1), 111-18
CODEN: EJBCAI; ISSN: 0014-2956

AB Factor VIII was **purified** 1200-fold from com. concs. by immunoaffinity chromatog. using an anti-(80-kDa light chain) monoclonal antibody. The different mol. forms isolated were subsequently sepd. and analyzed using fast protein liq. chromatog. and SDS-PAGE anal. The different **factor-VII** forms obtained, consisted of 80-kDa light chains, each being assocd. with 1 more-or-less fragmented heavy chain ranging over 90-210 kDa. The **specific activity** of these different forms was 7000 U/mg. At different stages of activation of factor VIII by thrombin, various forms were sepd. and identified. Activated complexes resulted from the assocn. of the 70-kDa light chain (generated from the 80-kDa light chain) with heavy

chains ranging over 90-210 kDa. Two different thrombin activation steps were characterized. The first step corresponding to the cleavage of the 80-kDa light chain led to a 6-fold increase in the procoagulant activity, and yielded a stable activated intermediate form. Compared with normal factor VIII, the ratio of von Willebrand activity to factor-VIII activity, measured in the activated fractions, decreased, indicating that von Willebrand factor dissocs. from factor VIII after proteolysis of the light chain by thrombin. In the second step, the 90-kDa heavy chain was cleaved into 2 polypeptides of 45 and 50 kDa, which were assocd. with the 70-kDa proteolyzed light chain, generating the final activated complex (45-50-70 kDa). The new intermediate forms described imply a new scheme for the multistep activation process of factor VIII.

AU Bihoreau, Nicolas; Sauger, Annick; Yon, Jeannine M.; Van de Pol, Hendrik

L6 ANSWER 30 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Process for the manufacture of concentrates containing **Factor VII** and Factor VIIa

SO U.S., 7 pp.
CODEN: USXXAM

AB A process for producing a conc. consisting of blood coagulation **factors VII** and VIIa with a **specific activity** of 500-3000 units/A280 is described. An aq. soln. of plasma proteins contg. **factors VII** and VIIa is adjusted to pH 6-8, brought in contact with an adsorbent having affinity for Ca-binding proteins, including **factor VII** in order to bind Ca-binding proteins. The absorbent consists of water-insol. divalent metal salts, e.g., hydroxyapatite; **factor VII** and factor VIIa are then eluted selectively. The eluate is adjusted to pH 3-11, contacted with an anion-exchange resine which has affinity for Ca-binding proteins, including **factors VII** and VIIa. **Factor VII**/VIIa are selectively eluted from the protein-bound adsorbent from the anion-exchange resin with a wash soln. contg. 0.1-0.45M NH4HCO3 and NaCl. The anion-exchange resin in the 2nd step consists of polysaccharide absorbent such as polygalactose, dextran, or cellulose resins. A plasma fraction contg. **factor VII** and VIIa was adsorbed onto DEAE Sephadex, the column was washed with NH4HCO3 until no further protein eluted at pH 7-7.8, the wash soln. was concd., the conc. was dild. into Tris buffer, and **factor VII**/VIIA were eluted with 0.15-0.30M phosphate buffer and the fraction contg. **factor VII** and VIIa were adsorbed to DEAE Sepharose, equilibrated with 0.02M MES buffer and **factor VII**/VIIa were eluted with 0.4M NaCl. The **factor VII**/VIIa thus obtained were free of clotting activity, i.e. free of factor II, factor IX, factor X.

IN Pancham, Nazreen

L6 ANSWER 31 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Affinity **purification** of plasma proteins: characterization of six affinity matrixes and their application for the isolation of human factor VIII

SO Thromb. Haemostasis (**1989**), 61(2), 234-7
CODEN: THHADQ; ISSN: 0340-6245

AB For the **purifn.** of coagulation factor VIII, 1,1'-carbonyldiimidazole-activated Sepharose CL-4B was functionalized with 2 aminoalkyl and 4-aminoalkyl-carbamylalkyl ligand-spacer combinations. The affinity matrixes interacted with human plasma. All affinity matrixes showed complete adsorption of factor VIII (>90%) and 3 aminoalkyl-carbamylalkyl Sepharoses gave factor VIII recoveries of 50-65% and a factor VIII prepn. with a **specific activity** of 1-2 U factor VIII/mg of protein. Furthermore, no fibrinogen, IgG, or albumin could be detected in the isolated factor VIII. Optimal results

were obtained using the di-methyl-aminopropyl-carbamylphenyl-Sepharose affinity matrix.
AU Te Booy, M. P. W. M.; Riethorst, W.; Faber, A.; Over, J.; Konig, B. W.

L6 ANSWER 32 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Prothrombin complex concentrates containing antithrombin III, blood coagulations factors and plasma, **purified** by adsorption to calcium phosphate
SO Ger. (East), 6 pp.
CODEN: GEXXA8
AB Prothrombin complex concs. contain in each transfusion unit >200 units of blood coagulation factors II, VII, IX, and X, 5-30 units antithrombin III, and 100 units heparin, stabilized by adsorption chromatog., using Ca3(PO4)2 as adsorbent. The concn. of I is 3.75-7.50 g per plasma unit, the pH of a I-plasma suspension is 7.2-8.2, the adsorbent-protein ppt. may be applied directly to the elution process or it may be washed at 10-30 vol. %/vol with a liq. contg. Tris 0.05, NaCl 0.18, and Chelaplex III mol/L at -2-20.degree. and pH 7.9-9.0. A soln. contg. 0.05 mol/L Na citrate and 0.01 mol/L Tris buffer at pH 7.2, at 6.8-7.5 vol. %/vol. plasma, was used to elute prothrombin complex and antithrombin III by a 2-step elution process. Erythrocytes were removed from edetate plasma by centrifugation and 50 mL of a stabilizer soln. contg. Chelaplex III 6.0, NaCl 3.5, glucose 21.5 g, and 1000 mL H2O were added for each 400 mL blood. Plasma (400 mL) was added to a suspension preferably contg. 2.0 g I.5H2O, 10 mL 0.15M NaCl in a 500mL blood preservation flask and shaken. I was removed by centrifugation and the ppt. was washed with 50 mL buffer contg. 0.05M Tris, 0.15M NaCl, and 0.01M Chelaplex III at pH 7.15, eluted, and the eluate was mixed with heparin (100 units/transfusion unit), the mixt. was frozen, and lyophilized. The product contained 220-250 units Factor II, X, IX, and 220-280 units **Factor VII**, and the **specific activity** was 1.2-2.0 units coagulation factor/mg protein. This product did not contain thrombin.
IN Dornheim, Guenter

L6 ANSWER 33 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI A lipoprotein-poor concentrate of coagulation **factors VII** and VIIA
SO U.S., 6 pp.
CODEN: USXXAM
AB Blood coagulation **factors VII** [9001-25-6] and VIIa [65312-43-8] are obtained in high purity by contacting an aq. prepn. contg. the factors with a lipoprotein-binding adsorbent and sepg. the coagulation factors, contacting the resulting lipoprotein-poor soln. with a divalent metal salt adsorbent having selective affinity for Ca-binding coagulation factors. Thus, Cohn fraction III was dissolved in distd. water, the pH adjusted to 7.5 with solid tris-base and lipoproteins were then pptd. with 60 mmol CaCl2 and dextran sulfate [9042-14-2]. The supernatant Ca was titrated with tetra-Na EDTA and back titrated with CaCl2 to slight Ca excess. NaCl was added to 0.5 M, the pH adjusted to 6.0, the supernatant applied to a column of hydroxylapatite [1306-06-5] equilibrated in 0.025 M morpholinoethanesulfonate at pH 6.0. The column was eluted with a 20-column vol. linear gradient of 0.4M Na2HPO4. The VII-contg. fractions were pooled, dild. 1:4 with distd. H2O and applied to a column of DEAE Sepharose. The **specific activity** of the final material was 1250 Units/A280. The recovery was 67%.
IN Zuffi, Timothy R.; Pancham, Nazreen

L6 ANSWER 34 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Concentrate of coagulation **factors VII** and VIIa
SO U.S., 6 pp.
CODEN: USXXAM

AB Blood coagulation **factors VII** [9001-25-6] and VIIa [65312-43-8] in relativity high purity are prepd. by contacting an aq. prepn. contg. these factors with a protein precipitant and sepg. the coagulation factors and other proteins. A divalent metal salt adsorbent was used to adsorb the Ca-binding coagulation factors. Thus, Cohn fraction III was suspended in 0.5M Tris, 0.15 M NaCl, and pH 7.5 buffer at 4.degree. and PEG 6000 was added to a final concn. of 3% (wt./vol.). The mixt. was centrifuged and the supernatant contg. **factor VII** (activity 40 units/mL) was collected and adsorbed onto hydroxylapatite [1306-06-5] which was equilibrated with 0.05 M Tris 0.15 M NaCl (pH 7.5-buffer). The resin was washed with an equilibrating buffer contg. M NaCl. **Factors VII** and VIIa were eluted at 0.15-0.3M phosphate concn. The fractions contg. these factors were adsorbed onto a Sepharose column and eluted with 0.15-0.35 M NaCl. The factors were pure and free from other clotting-activity factors. The **sp. activity** was 1059 as compared to the starting 2.5 value.

IN Pancham, Nazreen; Zuffi, Timothy

L6 ANSWER 35 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Alterations in the apparent tissue factor (thromboplastin) expression in HeLa cells by a cellular factor Xa inhibitor

SO Biochim. Biophys. Acta (**1983**), 761(1), 109-18
CODEN: BBACAQ; ISSN: 0006-3002

AB HeLa cells have undetectable tissue factor (thromboplastin) activity when measured by a 1-stage coagulation assay. In contrast, these cells accelerated the **factor VII**-catalyzed cleavage of factor X. The 2 assays gave similar results after either heating the samples to 100.degree. for 2 min or exposure to thrombin. Neither of these treatments altered the tissue factor activity of human foreskin fibroblasts, a cell type with high tissue factor activity. HeLa cells contain an inhibitor(s) directed against factor Xa but not thrombin. The inhibitor(s) was inactivated by exposure to thrombin or by heat treatment. Inhibition of factor Xa-catalyzed cleavage of a synthetic peptide was blocked by EGTA so the inhibition was apparently dependent on divalent cations. Inhibition was not accelerated by heparin. The inhibitor(s) was not protein C or other serine proteases since it was not inactivated by diisopropylfluorophosphate. The factor Xa inhibitor(s) was isolated from HeLa cells with an .apprx.500-fold increase in **specific activity**. After SDS-polyacrylamide gel electrophoresis factor Xa-inhibitory activity was recovered from a region corresponding to the major Coomassie-staining band at 43,000 daltons and in lesser amts. from regions corresponding to 26,000 and 17,000 daltons. Cellular inhibitors of coagulation may partially explain the low apparent tissue factor obsd. in some in vitro cells and may serve a regulatory role in limiting the expression of tissue factor.

AU Smariga, Paulette E.; Maynard, James R.

L6 ANSWER 36 OF 46 CAPLUS COPYRIGHT 2002 ACS

TI Urothromboplastin. Evidence for similarity between urothromboplastin and human brain thromboplastin

SO Paediatr. Paedol. (**1983**), 18(1), 73-80
CODEN: PAPAB5; ISSN: 0030-9338

AB Urothromboplastin (I) is a lipoprotein similar to human brain thromboplastin (II), the **specific activity** being dependent on the presence of the whole complex. I in normal human urine occurs in macroaggregates; therefore the substance is eluted from a Sepharose 2B column immediately after the void vol. and is found in the bottom of the tube after ultracentrifugation. In polyacrylamide gel electrophoresis, I does not enter the gel, but is eluted from the top of the gel. Na deoxycholate reduces the activity of I greatly; however,

after removal of this substance, the original activity is regained. There are similarities between I and II. In the same way as II, I acts in the extrinsic path of the coagulation system, and some evidence for binding of **factor VII** to I in the presence of Ca2+ was obtained. Anti-II antiserum neutralizes I, depending on the concn. of the antiserum. The same antiserum ppts. with I in the immunodiffusion method.
AU Mitterstieler, G.; Lechner, K.; Deutsch, E.; Margaritella, P.; Graninger, R.

L6 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Preparation of pure prothrombin by the cadmium(2+) method
SO Boerhaave Ser. Postgrad. Med. Educ. (**1975**), 10(Prothrombin Relat. Coagulation Factors), 93-8
CODEN: BSPEDP
AB Prothrombin was **purified** from plasma samples treated with 0.1M CdSO4 and Al(OH)3. The plasma mixt. was centrifuged to remove Al(OH)3 and other inorg. elements. The supernatant contained 1 mM CdSO4, .apprx.50% of the original prothrombin, and <0.5% of **factors VII**, IX, and X. Cd2+ was pptd. by oxalate and removed by centrifugation. Supernatant prothrombin was adsorbed onto Al(OH)3 and the sediment washed with 0.1M EDTA and 0.15M NaCl. Adsorbed proteins were eluted and the eluant chromatographed on DEAE-Sephadex columns. Prothrombin eluted as a single peak. The prepn. did not contain detectable amts. of other coagulation factors and appeared homogeneous by gel electrophoresis and antibody pptn. assays. The mol. wt. was .apprx.73,000, the N-terminal amino acid was alanine, and the **sp. activity** was 9 units/mg. No Cd2+ was detected.
AU Devillee, P. P.; DeGraaf, J. S.; Van der Voort-Beelen, J. M.; Bas, B. M.

L6 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI **Purification** and some characteristics of **factor VII** in human citrated plasma, glass activated serum, and cold activated plasma
SO Thromb. Res. (**1974**), 5(4), 539-56
CODEN: THBRAA
AB **Factor VII** was isolated from human plasma, glass-activated serum, and cold-activated plasma by batchwise adsorption with DE 11 cellulose and aluminum hydroxide gel followed by disc gel electrophoresis and DE 52 cellulose chromatog. Homogeneity was not attained by **sp. activities** equiv. to 30,000-100,000-fold **purifn.** were achieved. Activities of the **purified factor VII** prepns. were increased 450-800% by incubation with kaolin and aluminum hydroxide-adsorbed plasma. Mol. wts. for the 3 sources of **factor VII** prepns. were estd. by gel filtration as 58,000-62,000 daltons. The unactivated **factor VII** from plasma was isoelec. at pH 4.50-4.70, whereas the glass-activated serum **factor VII** was isoelec. in the pH region 5.35-5.55. Cold-activated plasma **factor VII** focused with 1 peak which coincided with traces of factor II at pH 4.60-4.70 and with 1 broad peak in the pH region of 5.10.
AU Laake, K.; Ellingsen, R.

L6 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Separation of clotting factors. II. **Purification** of human factor IX by isoelectric focusing
SO Biochim. Biophys. Acta (**1973**), 328(2), 456-63
CODEN: BBACAQ
AB Human prothrombin complex was subjected to isoelectric focusing. Factors II and IX were separated and recovered. The isoelectric point of factor IX was 4.1-4.37, that of factor II 4.57-4.70. **Factors VII** and X did not focus. The use of Sephadex G-100 gel filtration

of the prothrombin complex resulted in isoelectric focusing recovery of factor IX with no detectable factors II and VII and only a tract of factor X. Factor IX thus **purified** had a **specific activity** of 17.3 units (1730%) per mg protein, amounting to a 1082-fold increase in **specific activity** compared to original plasma.
AU Chandra, Sudhish; Pechet, Liberto

L6 ANSWER 40 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI The separation of autoprothrombin Ic from bovine prothrombin preparations
SO Can. J. Biochem. (**1964**), 42(9), 1249-62
AB Autoprothrombin Ic is a degradation product of **purified** prothrombin which is obtained when the enzyme autoprothrombin C is used for activation. A quant. method was developed for the assay of autoprothrombin Ic. Isolation procedures were developed for obtaining a single component. The **sp. activity** was 32,000-34,000 units/mg. tyrosine. The yield was about 4 mg. from 6 l. of plasma. By contrast with autoprothrombin C it did not by itself alter prothrombin activity. In the presence of lipids, Ca++, and Actlobulin it was a powerful procoagulant. Plasma and serum contain a substance that destroys the activity. The activity was also destroyed by reduced glutathione, iodoacetate, and ascorbic acid, but it was relatively resistant to SH-blocking agents. In the prothrombin utilization test **purified** autoprothrombin Ic gave prothrombin consumption with Stuart plasma and with **factor VII**-deficient plasma. With 0.5 .gamma. in the test mixt. (0.3 ml.) the prothrombin time of Stuart plasma was completely cor. With 60 .gamma. the clotting time was 8 sec.
AU Seegers, Walter H.; Kagami, Mitsuyasu

L6 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Proconvertin (**factor VII**). II. **Purification**
SO Scand. J. Clin. Lab. Invest. (**1964**), 16(1), 101-7
AB cf. ibid. 15(5), 450-6(1963). A procedure for the **purification** of **factor VII** (proconvertin) from human serum is described. The adsorbable coagulation factors were **purified** by elution with a linear gradient of 0.15M saline soln. (mixing bottle) and 0.3M Na citrate at pH 7.5 (reservoir) at 2.degree. (from a column prepd. by mixing BaSO4 with Sephadex G-25). Factors IX and X were eluted in the same fractions as VIII. These fractions were further fractioned on a diethyl-aminoethyl-Sephadex column with a linear gradient of increasing NaCl, and resulted in **factor VII** free of contaminations by prothrombin and factors IX and X. Final **purification** and concn.on BaSO4 resulted in a **specific activity** of about 18,000 units/mg. protein. This was a 1300-fold **purification** from serum if the possibility of activation during the procedure is not considered. The yield of **factor VII** activity was 40%. The **factor VII** activity was stable at 2.degree. for at least 1 month. When frozen at -22.degree., about 50% of the original activity was found on thawing. At room temp. about 80% of the activity was lost in 24 hrs.
AU Prydz, H.

L6 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2002 ACS
TI Preparation and properties of prothrombin
SO J. Biol. Chem. (**1959**), 234, 2857-66
AB cf. C.A. 50, 7291g. A procedure is presented for the prepn. of **purified** human and bovine prothrombin; it involves adsorption of plasma by BaSO4, elution with citrate, (NH4)2SO4 fractionation, and acid pptn. and yields material of high **sp. activity.** Although still contaminated with other clotting factors, some human fractions were obtained with activities which equal or exceed any

reported. Seitz filtration of bovine plasma before processing yielded a prothrombin fraction which could not be activated to thrombin biologically unless addnl. clotting factor(s), presumed to be **factor VII**, was simultaneously added. In this respect it resembled prothrombin derived from a patient with **factor VII** deficiency. The Seitz filter removes this essential nonprothrombin entity rather than altering the prothrombin mol., thereby rendering it biologically inert. This change does not take place with human plasma. Prothrombin prepns. which are readily activated, are contaminated with nonprothrombin factor(s) essential for prothrombin conversion to thrombin. The fact that human prothrombin fractions, still contaminated, can yield more than 2600 units of thrombin/mg. protein suggests that substantially higher **sp. activities** must be anticipated as ultimate purity is approached. Lower activities indicate contamination, denaturation, or other biol. impotence. Some biochem. and physiol. properties of these prothrombin prepns. are described, and the biol. implications pertinent to the characterization of prothrombin in the present status of its **purification** are presented.

AU Goldstein, Robert; Le Bolloc'h, Anne; Alexander, Benjamin; Zonderman, Estelle

L6 ANSWER 43 OF 46 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

PD 1995

TI [Profile of a highly **purified**, double virus inactivated **factor VII**].
EIGENSCHAFTEN EINES HOCHGEREINIGTEN, DOPPELT VIRUS-INAKTIVIERTEN FAKTOR-VII-KONZENTRATS.

SO Hamostaseologie, (1995) 15/1 (49-53).
ISSN: 0720-9355 CODEN: HAEMD2

AB Octavi SDPlus is a highly **purified**, double virus inactivated factor VIII concentrate. The **specific activity** in the final product is greater than 100 IU/mg of total protein. Stabilisation of the factor VIII is achieved by binding to its physiological carrier protein, the von Willebrand factor. Virus inactivation is carried out by a combination of a solvent and detergent treatment (Tri-[N-butyl]phosphate + Tween 80) and a modified pasteurisation (63.degree.C, 10 h). No evidence could be found for structural changes to the factor VIII/von Willebrand factor complex by this treatment. Virus validation of the manufacturing process resulted in a total log reduction factor of >13.5, >16.3 and >15.8 for the lipid enveloped viruses HIV, Herpes simplex and Sindbis, respectively, as well as >14.0 and >12.0, for the naked viruses HAV and polio, respectively. On this basis, the concentrate fulfils the requirements set out by Paul-Ehrlich-Institute for the virus safety of coagulation factor preparations. The pharmacokinetic parameters of the double virus inactivated preparation, Octavi SDPlus, are similar to those of other factor VIII preparations.

AU Biesert L.; Josic D.; Robinson S.; Helmich B.; Schwinn H.

L6 ANSWER 44 OF 46 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

PD 1993

TI Molecular defect in factor IX Tokyo: Substitution of valine-182 by alanine at position P2' in the second cleavage site by factor XIa resulting in impaired activation.

SO Biochemistry, (1993) 32/24 (6146-6151).
ISSN: 0006-2960 CODEN: BICHAW

AB Utilizing polymerase chain reaction and directly sequencing the amplified exon 6 of the factor IX gene derived from a mild hemophilia Bm patient, we have identified a T to C mutation at nucleotide 20 525. This point mutation predicted a Val182 to Ala substitution in the abnormal factor IX molecule, designated as factor IX Tokyo. The patient manifested a low factor IX activity and a moderately prolonged ox-brain prothrombin time

but a normal factor IX antigen level in plasma. Immunopurified factor IX derived from the patient was found to have a normal molecular weight but a reduced **specific activity** (23% of normal). Limited proteolysis by activated factor XI or by a snake venom-derived factor X-activating enzyme was considerably delayed, indicating the presence of structural alteration(s) most probably at or near the second enzyme-cleavage site. Once activated, however, factor IXa Tokyo was able to activate factor X normally and was inactivated by antithrombin III also in a normal fashion. The structural model of factor IXa and a docking model of factor IX and activated **factor VII** (factor VIIa) suggested that the Val182 to Ala substitution would not affect the local conformation of the catalytic domain. This mutation would rather loosen the fitness of the molecule into the substrate-binding pocket of factor VIIa due to a shorter side chain of the Ala substitution at the P2' position of the second cleavage site.

AU Maekawa H.; Sugo T.; Yamashita N.; Kamiya K.; Umeyama H.; Miura N.; Naka H.; Nishimura T.; Yoshioka A.; Matsuda M.

L6 ANSWER 45 OF 46 SCISEARCH COPYRIGHT 2002 ISI (R)

PD **1995**

TI HIGH-PURITY FACTOR-IX CONCENTRATES FOR TREATMENT OF HEMOPHILIA-B - RELATIVE PURITY AND THROMBOGENIC POTENTIAL

SO ACTA HAEMATOLOGICA, (**1995**) Vol. 94, Supp. 1, pp. 12-17. ISSN: 0001-5792.

AB Constituents other than factor UC have been implicated as etiologic agents for thrombotic complications in patients receiving prothrombin complex concentrates (PCCs). In vitro studies, in vivo animal models, and clinical evaluations in patients with hemophilia B indicate that high-purity factor IX concentrates contain significantly fewer potentially thrombogenic contaminants than PCCs. A recent in vitro study from our laboratory used highly sensitive assays to analyze the relative purity of these newer products. The following products were studied using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis and immunoblotting: Aimafix, AlphaNine-SD, Factor IX VHP, Immunine, Mononine, Nanotiv, and 9MC (now known as Replinine). The mean **specific activity** of the high-purity factor M products ranged from 68 IU factor IX/mg (Aimafix) to 246 IU factor IX/mg (Mononine). SDS-PAGE analysis under reducing and nonreducing conditions showed that Mononine had the fewest contaminating bands. The immunoblot to detect factor IX showed a dominant factor IX band for all products, visible Light chain of factor IX for all products except Aimafix, and another contaminating band visible at 49,500 daltons for all products except 9MC. High molecular weight contaminants were apparent for some products. Factor VIIa was detected in some lots of Immunine, Nanotiv and 9MC. Factor X and prothrombin contaminated Aimafix, AlphaNine-SD, Factor IX VHP, Immunine, Nanotiv and 9MC. Thus, Mononine, Nanotiv and 9MC demonstrated the highest purity but no product was totally free of contaminants.

AU LIMENTANI S A (Reprint); GOWELL K P; DEITCHER S R

L6 ANSWER 46 OF 46 SCISEARCH COPYRIGHT 2002 ISI (R)

PD **1991**

TI LIPID ASSOCIATION, BUT NOT THE TRANSMEMBRANE DOMAIN, IS REQUIRED FOR TISSUE FACTOR ACTIVITY - SUBSTITUTION OF THE TRANSMEMBRANE DOMAIN WITH A PHOSPHATIDYLINOSITOL ANCHOR

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (**1991**) Vol. 266, No. 32, pp. 21911-21916.

AB Full-length tissue factor (263 rTF) and three truncated forms have been expressed in human kidney 293 cells; 1) 243 rTF, which lacks the cytoplasmic tail, is fu]IY functional in the chromogenic assay and has a **specific activity** comparable with that of the full-length molecule, 263 rTF; 2) 219 rTF, which lacks both the

transmembrane and cytoplasmic domains, is not functional; 3) the third variant, referred to as TF-PI, is a fusion protein containing the extracellular domain of TF (amino acids 1-219) fused to the last 37 amino acids of decay-accelerating factor which contain a signal for attachment of a phosphatidylinositol membrane anchor (PI). TF-PI is a membrane-bound protein expressed on the cell surface. The PI anchor restores TF activity lost when the transmembrane domain is deleted from the 219 rTF variant. The ability of the PI anchor to restore activity to 219 rTF clearly demonstrates that while the transmembrane domain is not required for TF activity, lipid association is required.

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